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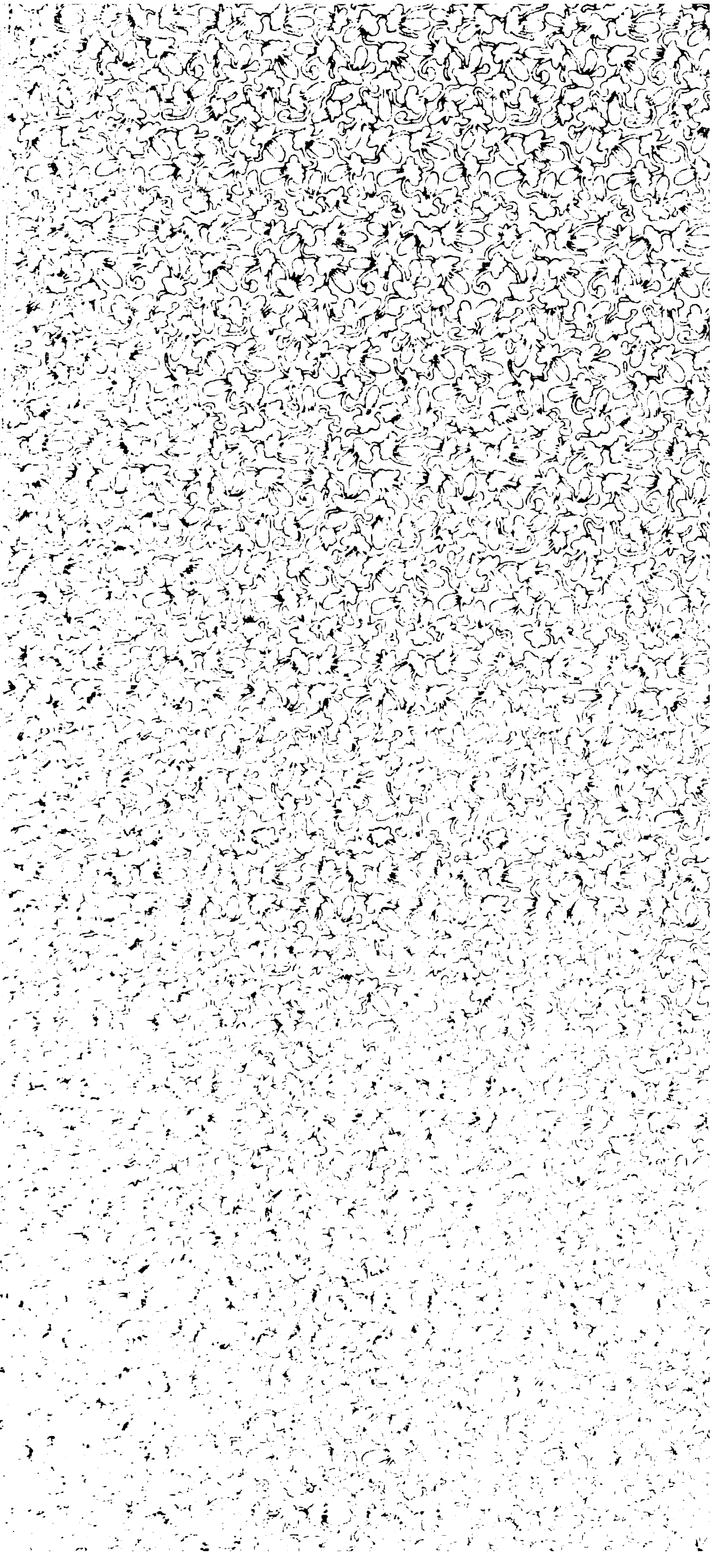

A TEXT-BOOK

OF

PHARMACOLOGY

AND SOME ALLIED SCIENCES

(Therapeutics, Materia Medica, Pharmacy,
Prescription-Writing, Toxicology, etc.)

BY

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PREFACE.

One of the achievements of the latter half of the century just closed has been the development of the study of the action of drugs along lines scarcely dreamed of formerly. This has been made possible mainly by recourse to animal experimentation; by methods analogous to those upon which the modern science of physiology is built; by replacing accidental observation by well-directed research. Our knowledge has thereby been placed on a footing of exactness, without which the application of drugs to the treatment of disease could only be empirical.

The ever-growing importance of this new science has made necessary a revolution in the methods of teaching and studying. To understand the facts furnished by experimentation, to appreciate the course of reasoning which led to them, to give their proper value to new observations, the attitude of the student must become somewhat that of the original investigator. Discourses on the application of drugs to the cure of disease must be supplemented by discourses on the physiologic action of the drugs, on reasons for these actions, and on the experiments upon which the stated facts are based. These again should be supported by demonstrations or laboratory work, if possible. A want of this acquaintance with experimental methods has served to delay the recognition of the importance of pharmacology. It has also hampered the more intimate relation of this science with applied medicine—a relation which could not fail to be of the greatest benefit to both. Nor does the usefulness of pharmacology stop when it has explained the action of drugs. It has placed the treatment of poisoning, as well as that of disease, upon a rational basis. It has thrown light upon the nature of many diseases which are really intoxications. It has furnished the other sciences with methods and instruments of research.

The subject of therapeutics has always been famous for the difficulty introduced into its study by the multiplicity

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of details with which it deals. A not insignificant service of pharmacology has been, that it enables us to arrange all the numerous drugs into a few groups. These groups are distinguished by a few typical actions, which vary only quantitatively in the individual members. To realize the advantage of this, one need but recall the groups of irritants or metals. By the old system, all the actions of these had to be enumerated under each member, whereas the pharmacologic grouping allows of one description, applicable to all. This needs only be supplemented by a few data concerning variations from the type. These groups can again be arranged in such order that the actions can almost be foretold from the relations. The relief from the severe tax of memorizing, obtained by this method, will be apparent to all.

The advantages of studying therapeutics in the light of pharmacology will scarcely need further recommendation. However manifest these advantages appear, it has greatly detracted from them that the facts furnished by pharmacology have been comparatively inaccessible. The bare statement of the conclusions of different observers is of use only if the underlying experiments are understood. Extensive text-books or technical journals are of use only to the specialist. Too great detail, indefinite statement, and conflicting theories only confuse the student. To treat the subject apart from its practical application makes this application difficult. To treat it as an adjunct to clinical therapeutics deprives it of the logical arrangement which constitutes one of its chief advantages. The two, although interdependent, are best separated in the teaching. The former, the clinical application, belongs properly to the practice of physic. On the other hand, the subjects of pharmacognosy, pharmacy, materia medica, prescribing, incompatibility, toxicology, etc., in so far as they have any place in the medical curriculum, are conveniently taught from the same chair as pharmacology.

My aim in writing this volume has been to meet these objections and indications.

I have attempted to give all the important pharmacologic facts. To facilitate their understanding and memorizing, they have been arranged in a systematic and logical manner, and the detailed account of the actions has been prefaced by a very brief summary. To bring out the more important points, liberal use is made of display type, rendering it possible to insert considerable matter intended only for reference, without making the book unwieldy.

The experiments and reasoning which have led to conclusions are given in detail whenever necessary. A section on laboratory work has been added, giving a few simple experiments, together with suggestions which will permit of making them much more extensive. These require but little apparatus, and no difficulty will be experienced in introducing them in schools with a limited number of students. With larger classes they may serve as a basis for demonstrations. The study of these experiments, even if they cannot be actually performed, will serve to render clear to the student many points which he would otherwise find it difficult to comprehend; their description should therefore form part of the text-book.

When the statements of different observers vary, or when several theories are advanced, stress has been placed on those which deserve preference. Others, which are manifestly erroneous, have often been omitted entirely. Whenever it has been possible to give a theory which accounts satisfactorily for a number of facts, this has been done.

To each group is attached a short section treating of its therapeutic application. This is further made prominent by numerous compilations of drugs which may be used to secure a given result; of the members, manner of action, and indications of the older therapeutic groups; and by a number of summaries giving the treatment of common pathologic conditions. These summaries are intended rather to point out the application of pharmacology to practice, leaving the detailed treatment of therapeutics to text-books on physic. Frequent cross-references are introduced to avoid repetition, but the latter is practised when it has seemed advantageous.

The subject of materia medica is a vexatious one in medical teaching, from the difficulty of deciding how much matter should be included. This is still more true of a text-book intended at once for study and for reference. I have aimed to limit the information to that which is likely to be of actual use in prescribing, and the preparations which deserve preference have been specially indicated by ⁂. Unofficial preparations in common use, or possessing advantageous features, have been freely introduced, preference being given to those of the "National Formulary."

The subject of pharmacy has been similarly restricted. Toxicology is discussed in conjunction with the pharmacology. A superficial knowledge of the course of toxicologic analysis is essential to the understanding of medicolegal questions. The identification of inorganic poisons receives sufficient treatment in text-books of chemistry. The organic poisons are generally omitted in these, and indeed often require pharmacologic experience for their recognition. A very brief outline of this subject has been given in a special chapter; similarly with pharmaceutic assaying.

I cannot lay much claim to originality in the subject-matter presented. It has largely been drawn from such standard authors as Schmiedeberg and others, and from technical journals. The pharmacologic groups are in the main those made classic by Schmiedeberg. In the compilation of the therapeutic sections I have been greatly aided by the works of Lauder Brunton and Kobert, and by the ordinary medical literature. For the methods of physiologic experimentation I am largely indebted to Stewart's "Physiology."

I am under great obligation to Dr. R. B. Metz and Dr. R. A. Hatcher for much valuable aid in the revision of the proofs.

CLEVELAND, O., *September, 1901.*

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EXPLANATION OF ABBREVIATIONS USED IN MATERIA MEDICA.

The sign ⁂ is reserved exclusively for the preparations most commonly employed.

When the name of a drug is preceded by a *, the drug is not official in the last edition of either the United States (*U.S.P.*) or the British (*B.P.*) Pharmacopœia. Preparations taken from the National Formulary, 1896, are denoted by (*N.F.*).

When the *official names* of the British and the U. S. Pharmacopœias are so similar that no confusion could arise through the omission, only one of these names is given, to avoid repetition. Similarly, when the *English name* does not differ from the Latin, important *synonyms* are always mentioned.

The name of the drug is followed by that of the plant, etc., from which a drug is derived, and this by its *order* and *habitat*.

Tinctura Digitalis — 15% — one-half Alcohol means that 100 c.c. of the tincture contain the soluble constituents of 15 Gm. of the drug, extracted with a menstruum consisting of one-half alcohol and one-half water.

Soluble in 750 parts of water means that 1 Gm. of the substance requires 750 Gm. of water for its solution.

Sp. g. = Specific gravity.

The *dose* is given in both the metric and common systems. A table is also given on the last page, which will facilitate the conversion of either system into approximate values of the other.

When the dose of the fluid extract is mentioned, that of the *crude drug* is omitted, the two being identical.

W = Water; A = Alcohol.

PART I.

THE PREPARATION AND PRESCRIBING OF MEDICINES.—TOXICOLOGIC ANALYSIS.

CHAPTER I.

ELEMENTS OF PHARMACOGNOSY.

PHARMACOGNOSY is that branch of science which treats of the physical and chemic character of drugs.

The crude organic drugs which form a large part of the materia medica are principally derived from the vegetable kingdom. All the different parts of a plant are employed. The active principle is often diffused throughout the plant, but is generally more abundant in one particular part, which is then used.

I. GROSS ANATOMY OF PLANTS.

1. **Underground Portions of the Plant.**—*Root* (*radix*): that part, generally devoid of chlorophyl (coloring-matter), which has not the power of producing leaves. Roots possess a bark, which is sometimes employed separately (sassafras, euonymus). If the underground portion does produce leaves, it is called *rhizome* (*rhizoma*). If part of the root serves for the accumulation of reserve food material, it becomes greatly thickened and is then called *tuber*.[1] If this accumulation takes place in the root-leaves, it forms a *bulb* (*bulbus*).[2] The lowest part of the stem of the plant is often thickened, and is then called *corm* (*cormus*).

2. **Portions Above Ground.**—When the whole plant, with the exception of the root, is used, it is termed *herb* (*herba* or *species*). This consists of stems, leaves, and often flowers or fruits.

---

[1] Potato.

[2] Onion.

Stem.—With herby plants this is called *stipes;* with larger plants it is transformed into *wood* (*lignum*) and is covered with *bark* (*cortex*). The outer (*epidermal*) layers of the older bark are always corky. Inside of this a secondary bark develops (*liber*).

The *leaves* (*folia*) may consist of a leaf-stem (*petiolus*) and the blade (*lamina*).

The shape of the leaves, the distribution of their veins, and the character of the edges are often of importance in distinguishing them.

The *flower* (*flos*) must be considered as a special modification of the leaves. It consists of the (usually green) *calyx* (parts = sepals) and a *corolla.*

The latter consists of the showy leaflets (petals) and the inconspicuous male and female elements (*stamens* and *pistil*). The former bear the fertilizing element in the form of granules (*pollen*). The pistil consists of the *ovary,* which develops the *seed,* and the *style* and *stigma,* which serve to receive the pollen. The calyx, corolla, and pistil or stamina may be wanting.

After fertilization the ovary develops into the *fruit* (*fructus*); this may also involve neighboring parts, especially the top of the stem, as in the apple, strawberry, etc.

The fruit consists of the outer portion, *pericarp,* and the seed (*semen*). The latter contains the embryo and nutritive material. It is protected by a more or less hard shell.

When the embryo begins to develop it differentiates into a rootlet, and a fleshy portion, *cotyledon,* which will form stem and leaves.

Certain organic drugs consist of the coagulated **juices** of the plant, and do not show any structure.

II. CHEMISTRY OF PLANTS.

Plants, like animals, consist of cells. These determine to a large extent not only the physical character, but also the chemic composition, of the drug.

The *cell wall* is much more conspicuous in plants than in animals. Its chemic composition is not uniform.

1. The *cell-contents* (which contain the nucleus) consist of protoplasm. This may present various **granular enclosures** consisting of proteids (*aleuron*), starch, fat, and mineral salts (especially calcium oxalate). They may be amorphous or crystalline.

Allied to the proteid enclosures are the *chlorophyl granules.* These consist of a colorless, spongy, proteid groundwork, containing in its meshes the chlorophyl pigment. The latter consists really of a mixture of green and yellow colors (chlorophyl and xanthophyl).

These chlorophyl granules are found mainly in the higher plants, and serve in the presence of light to assimilate CO_2, and consequently to form starch, etc. The chlorophyl is insoluble in water, but soluble in alcohol, ether, etc. During the process of drying, especially if this occurs slowly, the pigment is acted on by acids, etc., developed under these conditions, and undergoes various changes, usually becoming brown.

Other portions of the plant may also contain *coloring-matter of various nature.* (See p. 113, "Dyes.") These produce the brown, etc., color of the fluid preparations.

The *fat* seems to be deposited and formed much as it is in animals; *i. e.*, by the transformation of the protoplasm.

Fat and fixed oils are compounds of fatty acids and glycerin. The most important are:

FATTY ACIDS:	FATS:
Palmitic, $C_{16}H_{32}O_2$	Palmitin, $C_3H_5(C_{16}H_{31}O_2)_3$.
Margaric, $C_{17}H_{34}O_2$ $\left.\right\}$ $(= C_nH_{2n}O_2)$	Margarin, $C_3H_5(C_{17}H_{33}O_2)_3$,
Stearic, $C_{18}H_{36}O_2$	etc.
Oleic, $C_{18}H_{34}O_2$.	(Glycerin $= C_3H_5(OH)_3$).

They are greasy liquids or soft solids; when heated, they undergo decomposition, denoted by acrid vapors. They are insoluble in water or glycerin, sparingly soluble in alcohol, and freely soluble in ether, chloroform, benzin, turpentine, etc.

Fat may be seen in the cells either as drops or as crystals. The fat is most abundant in seeds, and may form more than half of their weight.

Starch $(C_6H_{10}O_5)_n$ is produced as one of the first stages in the assimilation of CO_2. It occurs in the form of granules, usually showing a laminated structure around a center (hilus). The character of this lamination, as well as the average shape and size of the granules, are important in distinguishing between different plants (Fig. 1).

Starch can be easily recognized by the blue color which it gives with iodin. It is insoluble in all the ordinary solvents, but with boiling water swells and forms a peculiar mixture (paste).

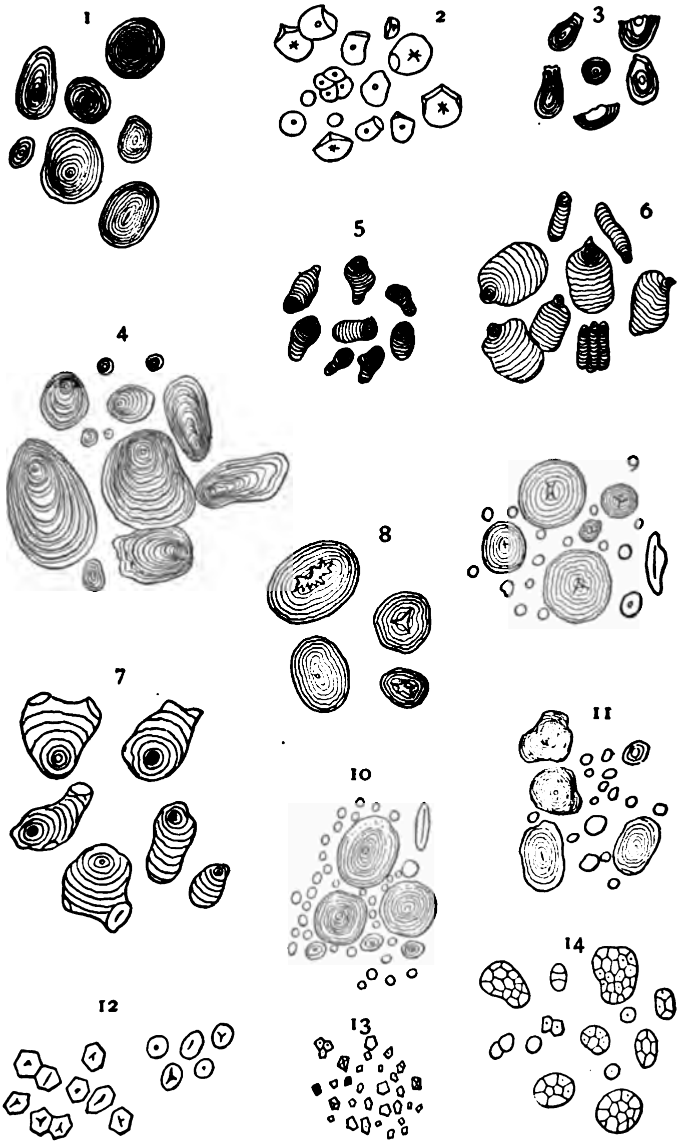


Fig. 1.—Microscopic appearance of different starches (uniform magnification) (Noël): 1, Arrowroot; 2, raw tapioca; 3, tapioca; 4, potato; 5, galanga; 6, East Indian arrowroot; 7, sago; 8, beans; 9, rye; 10, wheat; 11, barley; 12, Indian corn; 13, rice; 14, oats.

2. Besides these solid enclosures, the protoplasm may contain a large number of **substances in solution.** These may, however, also occur as precipitates under special conditions. In dried plants they occur, of course, as solids.

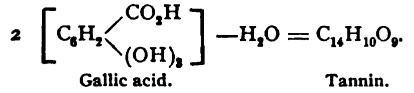
Tannins.—These are somewhat ill-defined compounds, their composition being little understood. They probably do not all belong to the same chemic group, although they contain the benzol ring. They possess certain properties in common: They form insoluble compounds with iron salts, with proteids, alkaloids, gelatin, etc. With connective tissue they form an extremely insoluble and impenetrable compound, leather. On account of the reaction with proteids, etc., they possess an astringent action.

The precipitate formed with iron has a blue color with certain tannins, a green color with others, and this seems to some extent to be connected with differences in their composition. This is not, however, sufficient to form them into two groups, since the color varies with the reaction of the liquid.

Tannins are soluble in water and in alcohol, but since they form insoluble compounds with so many substances, they frequently occur in plants in granular form.

They are easily decomposed, some yielding glucose as one of their decomposition products, others a class of bodies greatly resembling resins, and called phobaphenes. Others yield pyrocatechin on destructive distillation.

Gallic acid is related to the ordinary (oak) tannin:



$$2\left[C_6H_2\begin{matrix}\diagup CO_2H\\ \diagdown (OH)_3\end{matrix}\right] - H_2O = C_{14}H_{10}O_9.$$

Proteids.—All the different classes are represented. They may be characterized by the biuret or Millon's reactions.

Sugar.—The various forms of sugars enjoy a wide distribution in the vegetable kingdom, and occur as canesugar, dextrose, levulose, and others. Some of these reduce copper in alkaline solution. All turn the plane of polarized light. They are soluble in water; much less so in alcohol. The most important types are:

Mannite, $C_6H_{14}O_6$.
Glucose, $C_6H_{12}O_6$.
Maltose and saccharose, $C_{12}H_{22}O_{11}$.

Intermediate between starch and sugar are dextrin and gums; the latter are largely pathologic.

Resins are compounds of uncertain compositions, non-volatile, soluble in alcohol, etc., insoluble in water. They are contained in special vessels, from which they are usually obtained as exudations after incising the plant. When they occur mixed with essential oils, they are ***natural oleoresins***; when mixed with gums, ***gum-resins***. If they contain aromatic acids (cinnamomic, benzoic, etc.), they are called ***balsams***.

The most active principles of the plant also exist largely in solution. Of these, the most important are the *alkaloids*. (See p. 151.)

Glucosids are those principles which, subjected to the action of ferments or of acids, yield glucose as one of their decomposition products. Many do not contain nitrogen. But little is known about the chemic structure.

This holds true still more of other active principles, such as *bitter substances*, *saponins*, etc.

Proximate principles are definite organic chemic constituents, and are the purest form in which an organic substance can be isolated, without changing its nature.

Thus, morphin (not morphin sulphate).

Neutral principles are those which do not possess acid or basic characters.

Bitter principles are those which possess a bitter taste (alkaloids are not usually included in this class).

Active principles are those which determine the action of the drug.

Resinoids are principles soluble in alcohol and insoluble in water.

The juice of the plant contains dissolved in it a large number of organic compounds, such as *alcohols*, *aldehyds*, *ethers*, *acids*, *aromatic bodies*, etc.

Plants almost always contain *coloring-matter*, the chemic nature of which is often not known.

They also contain a fair amount of *mineral salts*, which remain as ashes when the plants are incinerated; these salts seem to be combined largely with the protoplasm, and exist partly dissolved, partly as crystals. Growing tissues are always richer in salts than those fully developed.

By *extractive matter* is meant the smeary mass of unknown composition which remains after evaporating any extract from which the important constituents have been removed.

III. THE CELL.

The form and arrangement of the cell wall will determine the histology of the plant.

1. This **cell wall** consists originally of *cellulose*. This cellulose is chemically an isomer of starch, having the elementary formula $(C_6H_{10}O_5)_m$. It is insoluble in all the ordinary solvents, and is not affected by boiling water. It dissolves without change in Schweitzer's reagent (ammoniated solution of copper sulphate). In older cells it is often modified by the introduction of allied molecules: wood (lignin) or cork (suberin). The cellulose may also undergo a retrograde metamorphosis into gum or pectin.

A means of distinguishing between these compounds is the action of iodin after concentrated sulphuric acid: the tissue is treated with a drop of concentrated H_2SO_4, washed, and then placed in iodin solution; this will give a blue color to cellulose, but not to lignin or cork. Cellulose does not easily take up pigments, lignin does. Cork is very resistant to reagents and impermeable to water, and hence protects the plant against evaporation and chemic injury.

Under certain conditions cellulose seems to be converted into gum or pectins. This transformation may also involve the cell content. It occurs to some extent normally in certain tissues, but may become extremely abundant as the result of a pathologic process. The chemistry of these gummy substances is but imperfectly understood, but they belong to the carbohydrate group.

Gums and pectins are substances giving slimy solutions with water; they are insoluble in alcohol; they yield reducing sugars when boiled with dilute acids.

2. **Forms of the Cell.**—The cell may increase in size and in thickness, and assumes varying forms. The growth in thickness may remain confined to the walls, so that the lumen may be almost abolished. In either case it may not be uniform over the whole surface of the wall, and in this way depressions (pits) or elevations may be formed. The latter may assume various shapes, and occur as spirals, network, etc. (Figs. 2 and 3).

If the cell wall becomes very thick and the lumen correspondingly small, the result is a *stone cell* (Fig. 4).

3. The two **ground forms** of vegetable cells are:

Parenchyma (Fig. 5, and Fig. 6, *b*): Thin-walled cells of nearly equal diameters, rich in protoplasm, constituting the soft tissues.

Prosenchyma (Fig. 8): Thick-walled cells, lengthened, poor in protoplasm, found in all hard tissues.

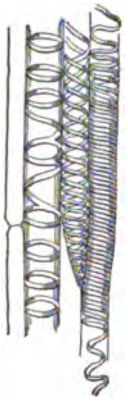


Fig. 2.—Spiral cell from squills (Flückiger and Tschirch).

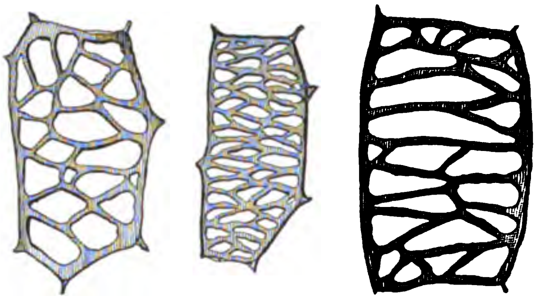


Fig. 3.—Reticular thickening of cell wall (Flückiger and Tschirch).

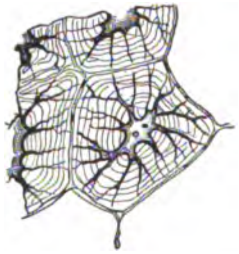


Fig. 4.—Stone cells from nutshell (Flückiger and Tschirch).

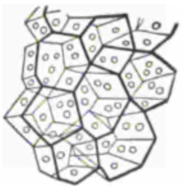


Fig. 5.—Parenchyma from elder pith (Flückiger and Tschirch).

IV. THE TISSUES.

The cells are united into tissues, which may be classified, according to structure and functions, into:

1. *Dermal:* for external protection.
2. *Supporting:* to give solidity.
3. *Assimilation:* for assimilation of CO_2.

4. *Conduction:* for the conveyance of juices.

5. *Storage:* for accumulation of reserve stock of water and nutritive material.

6. *Aeration:* for the conveyance of air.

7. *Glandular:* For the elaboration and storage of secretions.

1. Dermal Tissues.—The *epidermis* (Fig. 6, *a*) consists, in the higher plants, of one or more layers of flattened cells, generally possessing thickened walls, and covered by a structureless resistant membrane, *cuticle*.

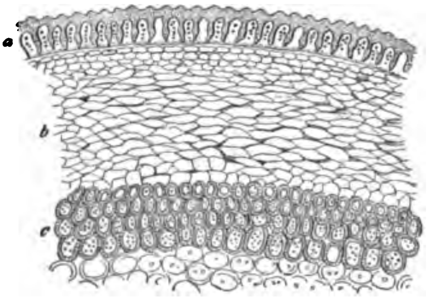


Fig. 6.—Fruit-shell of colocynth: *a*, Epidermis; *b*, parenchyma; *c*, sclerenchyma (Flückiger and Tschirch).

The epidermic cells may be transformed into *hairs* (trichomata) (Fig. 7). These may take on *glandular* functions (elaboration of the essential oils, resins, or gums); or they may be transformed into *spines;* but the latter generally contain wood also.

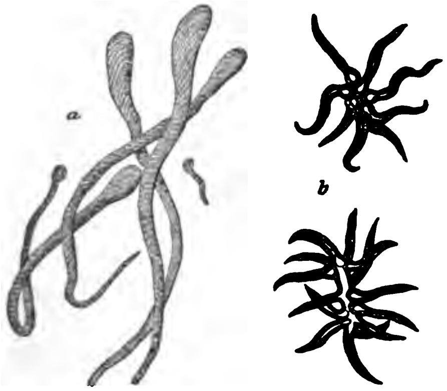


Fig. 7.—Hairs from mullein flowers: *a*, From stamina; *b*, from petals (Flückiger and Tschirch).

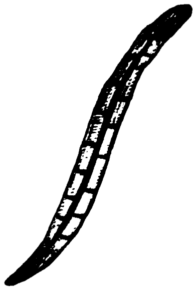


Fig. 8.—Bast cell from cinchona-bark (Flückiger and Tschirch).

This epidermis is the only covering of delicate plants; with the larger species it becomes insufficient. In these it is reinforced by the development beneath it of the *periderm*, which consists of cork cells. These are also flattened, thick-walled cells; they contain air and no protoplasm.

2. **Supporting Tissues.**—In younger tissues this function is borne by polygonal cells (*collenchyma*) with rather thick walls and containing protoplasm. In fully developed plants this is replaced by *bast cells* (*scleroids*) (Fig. 8); *i. e.*, long cells, similar to stone cells, with very thick walls and small lumen, containing air. They are variously arranged, occurring either isolated or combined into definite structures.

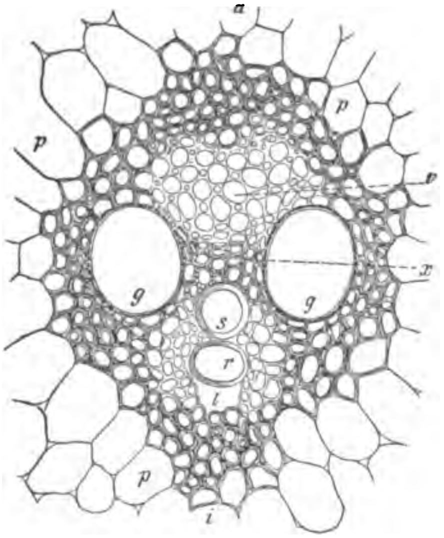


Fig. 9.—Transverse section through fibro-vascular bundle of maize stem: *a*, Exterior; *i*, interior; *p*, ground tissue; *r*, ring-vessels; *s*, spiral vessels; *g*, dotted vessels; *l*, intercellular cleft; *x*, wood cells; *v*, phloem (Sachs).

3. **Assimilation Tissues** (for CO_2).—These consist of the cells containing chlorophyl. Since assimilation of carbon occurs only in the presence of light, such cells are only found on exposed portions, especially in the leaves, and here on that side of the leaves turned toward the sky. The cells are of the parenchyma type, and are rich in protoplasm in which chlorophyl granules are embedded. The cells are usually arranged in palisade form.

4. **Conducting System.**—The leaf-ribs, stems, and roots of plants are traversed by long fibrous structures, the *fibro-vascular bundles* (Fig. 9). These consist of a number of conducting elements, surrounded and supported by bast cells. The former consists of several structures which may not all be present in the same bundle. These are:

(*a*) *The vessels proper.* These are long tubes, formed through the disappearance of the separating wall of adjoining cells. The walls of these tubes show various thickenings, which serve to classify them into ringed, spiral, ladder, etc., vessels. (Fig. 9, *r*, *s*, *g*.)

(*b*) The *tracheids* (wood cells). Each tube consists of a single long cell with rather heavy walls. These two sets of vessels serve for the conduction of water. (Fig. 9, *x*.)

(*c*) *Wood parenchyma* (phloem). Short, thin-walled, protoplasmic cells, serving for the conduction and storage of carbohydrates. (Fig. 9, *v*.)

The *wood* (*lignum*) consists of these three elements, and of bast cells; all these are, on the whole, arranged in the long axis of the stem, but are traversed radially by rows of parenchyma cells (*medullary rays*). The youngest layer of the wood in dicotyledenous plants is the *cambium*, consisting of flat parenchyma cells.

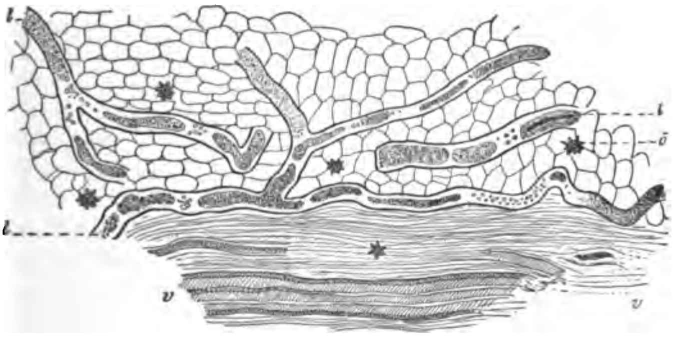


Fig. 10.—*l*, Lacteal vessels; *o*, calcium oxalate crystals; *v*, vascular bundles (Flückiger and Tschirch).

(*d*) Another element of the fibrovascular bundles is formed of the *sieve tubes*, very long cells, whose walls are formed by delicate membranes pierced with holes. They serve for the conduction of the albuminous elements.

5. Storage System.—Arrangements for the storage of reserve food material exist in the most varied organs. These reserve foods consist usually of solid and sparingly soluble substances: starch, fat, proteids, etc. Water is also stored. The storage takes place in the bodies of the cells forming these structures.

6. System of Aeration.—The gaseous metabolism of plants is very important. An extensive system exists for the penetration and distribution of gases. The epidermis, especially on the under surface of the leaves, is provided with pores (*stomata*), usually guarded by special cells, and these communicate with clefts in the tissue.

7. Glandular System.—This consists partly of cells, partly of tubes. The latter may be formed by the breaking-down of cell bodies, or as regular ducts, similar to those found in animal glands.

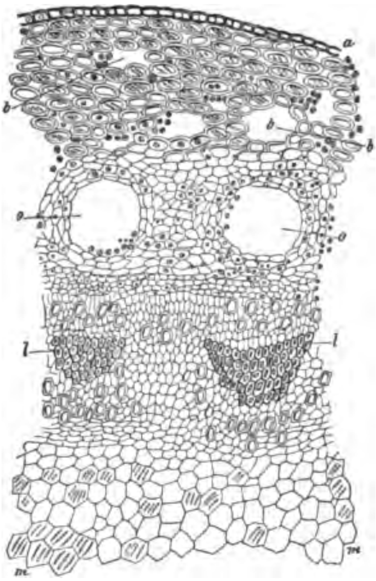


Fig. 11.—Oil spaces in transverse section of rhizome of *Arnica montana*: *l*, Wood-bundles; *o*, oil spaces; *b*, in process of formation by tearing of the ground tissue; *a*, epiblema (root-epidermis). Free oil drops are to be seen in the neighborhood of the oil spaces.

The *glandular cells* serve especially for the elaboration and storage of *ethereal oils*. They occur isolated and have a more or less globular form. Cells also serve for the elaboration and storage of mucilaginous and resinous substances.

Tubes.—The tubes for *milk juices* are partly conducting, partly glandular in function. They arise through the absorption of the separating membrane of cells, like the vessels of the vascular bundles, but usually occur isolated (Fig. 10). These cells were originally filled with secretion: *caoutchouc* (differing from resin in being insoluble in ether), *alkaloids* (opium), *resins*, *oils*, or *balsams*. The side wall of the cell may also disappear, so that the contents lie in an intercellular space—resin or oil spaces (*e.g.*, oil of lemon)—(Fig. 11, *o* and *b*).

These differ in the manner of their formation from the *secreting spaces* (Fig. 12, *hg*), which were never cells, but represent from their origin ducts like those found in animal glands, and are surrounded by special parenchymatous secreting cells (Fig. 12, *c*). This formation is especially common in the umbelliferæ, compositæ, and coniferæ, in which they contain resins and essential oils.

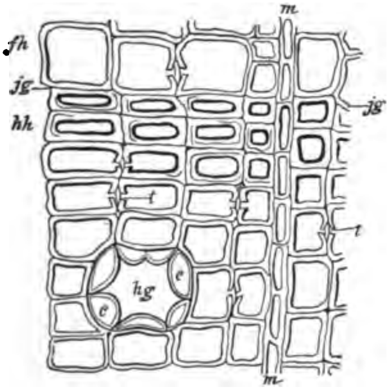


Fig. 12.—Cross-section of pine-wood: *jg*, Annual rings; *fh*, spring wood; *hh*, fall wood; *hg*, resin duct; *c*, secreting cells; *t*, pores; *m*, medullary rays.

CHAPTER II.

PHARMACY; METROLOGY.

1. Definition and Objects.—*Pharmacy* deals with the preparation and compounding of drugs for the purpose of administration.

The necessity for such an art will be readily understood. Drugs may be divided according to their origin into mineral, vegetable, and animal drugs. The last two are often too bulky to be conveniently used, and the substances which determine their action are often in such a condition that they can not readily be separated in the body, and so can not develop their action. Further, one drug alone does not usually meet all the indications in a disease, and when several are given it is necessary to combine them in such a way that they may not interfere with one another, either chemically or mechanically. Lastly, having chosen and prepared the drugs in a proper manner, and having decided how to combine them, it is highly desirable to give them in such a form as will be least objectionable to the taste, smell, or sight of the patient.

These constitute the objects of pharmacy: the separation of the active principles of drugs, their combination, and the putting of them in a pleasant form. In regard to the preparations, only those of the drugs of organic origin—the "Galenics,"[1] so called—will be treated of in this place. The preparation of inorganic compounds belongs more strictly to the domain of chemistry.

A certain degree of uniformity in the strength and preparation of pharmaceutic products is absolutely indispensable. Accordingly, practically all civilized countries have standards established by law, to which the drugs and preparations in the shops must conform. The book in which these standards are published is usually called the *Pharmacopœia*. That of the United States was first published in 1820, and is revised every ten years by a committee of physicians and pharmacists. Preparations made in conformity to it are called official.

Many unofficial preparations, not contained in it, are also in current use. The real basis of the strength of all preparations should, of course, be founded upon actual tests of their pharmacologic action. But this has not been found practicable in many cases. When the important constituents are well known and of constant activity and composition, every purpose is served by determining the percentage of these ingredients by a process of assaying. (See p. 85.) But even this is not practicable in many cases, so that the strength of many preparations is purely empirical; they are made from so much of the drug, diluted to a given amount. Crude as such a method may be, since it takes no account of the natural variability in active constituents of the drug itself nor of the difference in the skill of the manufacturer in extracting these constituents, it is none the less useful. For this purpose, then, it is only necessary to weigh and measure the various ingredients, and, for the rest, to follow to the letter the directions for the manipulations.

A discussion of the elementary principles of metrology, the science of weights and measures, then, forms the first topic treated of in this chapter.

2. **Metrology.**—Formerly every country, even every State,

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[1] "Galenics" are, strictly speaking, medicines prepared after the formulas of Galen. The term is now used to designate standard preparations containing one or several organic ingredients.

and some cities, had their own system of weights and measures, resulting in endless confusion and loss of time. This state of affairs still exists to some extent. In the United States and Great Britain no less than five different systems are in common use. It is a hopeful sign that the United States Pharmacopœia has decided to employ the metric system. This system originated in France near the close of the last century. It has been adopted in science to the exclusion of all others, and possesses a number of advan-

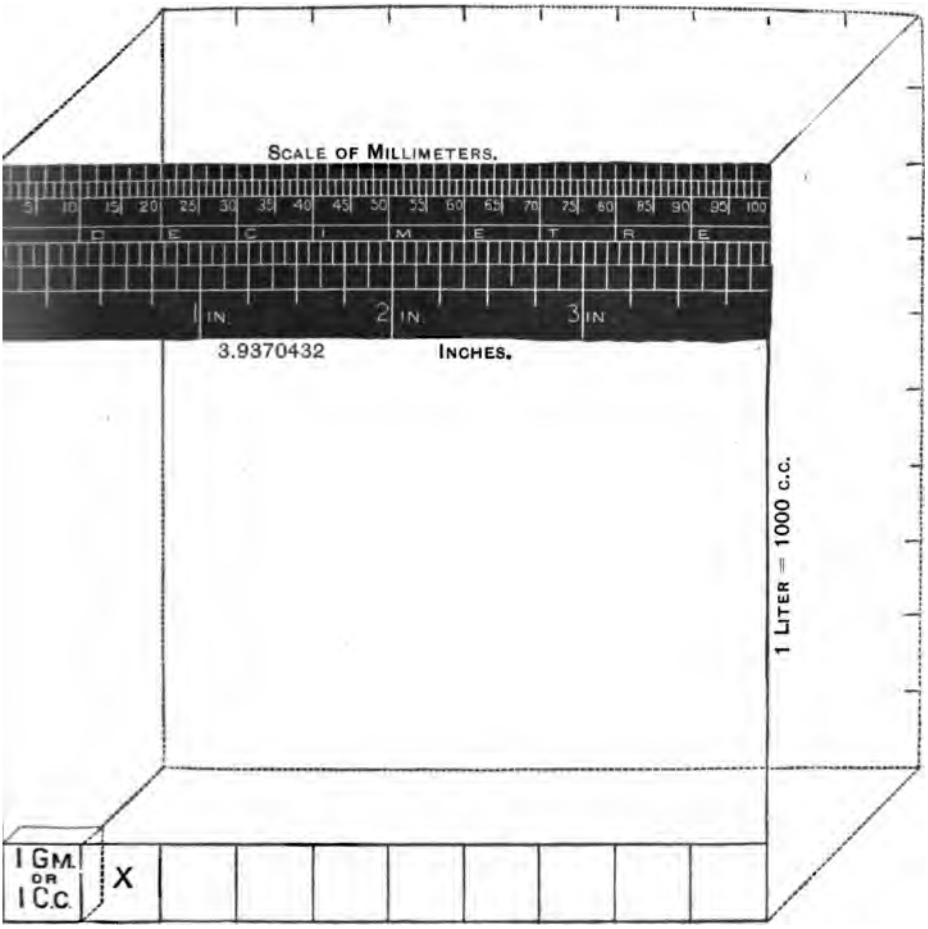

Fig. 13.—Metric diagram—comparison of measures of length, capacity, and weight (Coblentz).

tages which will be better appreciated when all the current systems have been considered.

The Metric System.—This is based on the decimal system, and has for the unit of all measure the measure of length, the meter (M.), the forty-millionth part of the meridional circumference of the earth. This is divided into 10, 100, and 1000 parts, called respectively decimeter (dm.), centimeter (cm.), and millimeter (mm.).

The contents of a cube whose edges measure a decimeter form the unit of capacity (Fig. 13), the liter (L.). The thousandth part of this is a cubic centimeter (c.cm., or, briefly, c.c.). The unit of weight is given by the weight of a liter of distilled water at 4° C. and 760 mm. pressure: this is the kilogram (Kg.). A thousandth part of this is a gram (Gm.). A quantity ten times the unit is expressed by prefixing the Greek numeral Deca; one hundred times, Hecto; one thousand times, Kilo. The tenth part of the unit is expressed by prefixing the Latin numeral deci; one-hundredth, centi; one-thousandth, milli.

Thus:

1000 Gm. = Kilogram (Kg.)
100 " = Hectogram (Hg.)
10 " = Decagram (Dg.)
1 " = Gram (Gm.)
0.1 " = decigram (dg.)
0.01 " = centigram (cg.)
0.001 " = milligram (mg.)

In quantities including several denominations only one unit is used: thus, 1.234 Kg. would be read as 1234 Gm.; 0.002 Gm. as two milligrams, etc. It will be seen that in the abbreviations capital letters are used for the units and larger, and small letters for fractions of units. The quantities are always denoted by Arabic figures placed before the appellation. Fractional parts are always converted into decimal fractions.

In continental Europe the liquid measure is very little used in pharmacy, liquids being usually weighed.

Whilst the metric system has now been adopted as the pharmaceutic standard, other systems—the so-called common systems—are still in vogue for prescriptions and in commerce. These have an arbitrary unit, the *grain*.

The denominations are the following:[1]

APOTHECARIES' OR TROY WEIGHT.

(Used in Prescriptions.)

Grain (gr.)
[Scruple, (℈) = 20 grs.]
Drachm, (ʒ) [= 3℈] = 60 grs.
Troy ounce, (℥) = 8ʒ = 480 grs.
[Troy pound = 12℥ = 5760 grs.]

(℥j of water under standard conditions measures 505¼ minims.)

AVOIRDUPOIS WEIGHT.

(A System Used in Commerce.)

Grain = same as Troy grain.
Ounce (oz.) = 437½ grains.
Pound (lb.) = 16 ozs. = 7000 grains.
Ton = 2000 lbs.

UNITED STATES APOTHECARIES' OR WINE MEASURE.

(Used in United States for both Prescription and Commercial Purposes.)

Minim (♏) (approximately equal to one drop or to one grain of water—more exactly, 0.95 grain).
Fluidrachm (flʒ) = 60 ♏.
Fluidounce (fl℥) = 8 flʒ = 480 ♏ (fl℥j of water under standard conditions weighs 456⅜ grains).
Pint (pt., or Octarius, O) = 16 fl℥ = 7680 ♏.
Quart (qt.) = 2 pts. = 32 fl℥.
Gallon (gal., or Congius, C) = 8 O = 128 fl℥ = 61,440 ♏.

A gallon holds 231 cubic inches.

Another system of liquid measure is in use in *Great Britain*, and must not be confused with the American system. It is the

IMPERIAL MEASURE.

			United States System.
Minims (min.)	=		0.96 ♏
Fluidrachm (fl.dr.)	=	60 min.	= 0.96 flʒ
Fluidounce (fl.oz.)	=	8 drachms	= 0.96 fl℥
Pint (O)	=	20 fluidounces	= 1.2 O
Gallon (C)	=	8 pints	= 1.2 C

In writing the apothecaries' measure in prescriptions, the figures are written in the Roman system and placed after the appellation. Thus, gr. xx, not 20 grs. The ones are always dotted, and the last one is formed like a j: thus, ʒiij, ℥vj, etc. The fl. before the sign is often omitted with liquids.

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[1] Those in square brackets are practically obsolete.

Fractions are written as common fractions: gr. $\frac{1}{10}$, not gr. 0.1.

Popular Measures.—These are formed of utensils commonly found in the household, and are, of course, very inexact. They should be displaced by graduated medicine glasses, which can now be obtained very cheaply.

The usually accepted equivalents of these measures are:

1 drop (gtt.)	=	1 minim [1]	=	0.06 c.c.
1 teaspoon	=	1 flʒ [2]	=	4.0 c.c.
1 dessertspoon	=	2 flʒ	=	7.5 c.c.
1 tablespoon	=	4 flʒ (½℥)	=	15.0 c.c.
1 wine-glass	=	2 fl℥	=	60.0 c.c.
1 tea-cup	=	4 fl℥	=	120.0 c.c.
1 tumbler	=	8 fl℥	=	240.0 c.c.
1 knifepointful (tableknife)	=	15 to 30 grs.	=	1.0 to 2.0 Gm.

3. The **units of temperature** may also be treated in this place.

The scientific scale is the *Centigrade* or Celsius. In this the range between the freezing-point of water (0° C.) and its boiling-point (100° C.) is divided into 100 parts. In the *Fahrenheit* scale, in common use, the freezing-point of water is 32° F., the boiling-point 212° F., and the range, therefore, 180° F.

Each degree Centigrade therefore $= \frac{180}{100} = \frac{9}{5}$° F.
Each degree Fahrenheit $= \frac{5}{9}$° C.

The *conversion* of one scale into the other may be done by the following *rules:*

To convert degrees Centigrade into Fahrenheit: multiply by $\frac{9}{5}$ and add 32.

To convert degrees Fahrenheit into Centigrade: subtract 32 and multiply by $\frac{5}{9}$.

4. The **advantages of the metric system** will now be manifest.

1. The unit is a final and natural one, which can always be verified.

2. There is a simple relation between linear, solid, and liquid measures.

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[1] As a matter of fact, the size of a drop varies greatly according to the nature of the fluid and of the container; there may be from 50 to 150 to a fluidrachm.

[2] Really from ½ to 2 flʒ.

3. The decimal feature determines great ease in multiplications, since only a change of a decimal point is required to change one denomination into another. It is also much easier to write the quantities.[1] Calculations involving specific gravity are also much more easily made.

4. The system is universally known and easily understood.

5. Table I.—Equivalents of Metric and Common Systems.—

SPACE.

1 meter = 39.370 inches.	1 inch = 0.0254 M. = 2.54 cm.
= 3 ft. 3.370 inches.	1 ft. = 30.227 cm.
= 1 yd. 3.370 inches.	1 yd. = 90.681 cm.

CAPACITY (UNITED STATES).

1 c.c. = 16.23 ♏.	1 ♏ = 0.06161 c.c.
1 L. = 33.815 fl℥.	1 flʒ = 3.7 c.c.
= 2.113 pts.	1 fl℥ = 29.572 c.c.
= 0.2641 gal.	1 pt. = 0.4731 L.
	1 gal. = 3.7848 L.

CAPACITY (BRITISH).

1 L. = 1.760 pints.	1 pint = 0.5679 L.
= 0.2209 gallons.	1 gallon = 4.5435 L.

WEIGHT.

1 mg. = $\frac{1}{64}$ gr.	1 gr. = 64.8 mg. = 0.0648 Gm.
1 Gm. = 15.432 grs.	1ʒ = 4 Gm.
= 0.03527 oz. Av.	1 oz. Av. = 28.3495 Gm.
= 0.03215 ℥ Troy.	1 ℥ Troy = 31.1035 Gm.
1 Kg. = 2.2046 lbs.	1 lb. = 0.4536 Kg.

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[1] An example will make this clearer: Take 40 Gm.: in the United States system this must be written ℥j ʒij gr. xvij. Should it be necessary to calculate five times this quantity, one multiplication will suffice with the metric system: 5 × 40 = 200 Gm. But with the Apothecaries' system, the operation would be much more complicated:

5 × ℥j ʒij gr. xvij = ℥v ʒx gr. lxxxv

This must be reduced:

℥v = ℥v
ʒx = ℥j ʒij
gr. lxxxv = ʒj gr. xxv
Answer = ℥vj ʒiij gr. xxv

6. Examples in Weights and Measures:

1. Express in ℥, ʒ, and grs.: 2000 grs.
2. " " gal., pts., fl℥, flʒ, and ♏: 200,000 ♏.
3. " " yds., ft., and inches: 200 inches.
4. " " Centigrade: 40°, 20°, 0°, 10°, 30°, 60°, 100° and 180°, Fahrenheit.
5. " " Fahrenheit scale: 40°, 20°, 0°, 10°, 30°, 60°, 100° and 180° Centigrade.
6. " " Metric system (*a*) 2 yds., 2 feet, and 2 inches.
   (*b*) 2 gals., 2 pts., 2 ℥, 2 ʒ, and 2 ♏.
   (*c*) 2 lbs., 2 ozs., and 2 grs. Avoirdupois.
   (*d*) 2 ℥, 2 ʒ, and 2 $\frac{1}{100}$ grains Troy.
7. " " United States System (*a*) 2,222 M.
   (*b*) 22 mm.
   (*c*) 2,222 L.
   (*d*) 22 c.c.
   (*e*) 2,222 Kg.
   (*f*) 22 mg.
   (*g*) 22 Gm.

Use common fractions for quantities less than inch, grain, or minim.

INSTRUMENTS AND METHODS OF METROLOGY.

7. Weighing.—In determining the weight of a body, we balance the force which it exerts by virtue of its gravity, against another known force.

This is done by means of a balance, or, as it is called when used for larger masses, a scale. These are constructed on either the spring or lever principle.

The *spring balance* does not allow of any great accuracy, but has the advantage of cheapness and is very convenient.

The extent to which a spring is stretched by a given weight is determined experimentally, and a scale constructed in this manner (see Fig. 14).

The *lever or beam balance* compares the weight of a substance with a known weight suspended from the other side of the fulcrum. The arms of the lever may be *equal* (Fig. 15), when the weights on the two sides must also be equal in order that they may balance (equal-arm balance). The fine scales are usually constructed on this principle.

Or the arms may be of unequal length, when the weight is given by the formula L W = L′ W′; where L = length of beam and W the weight: *i.e.*, if W is 1 and L is 1, then if L′ = 2, W′ will be ½.

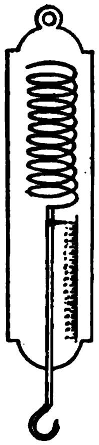

Fig. 14.—Diagram of spring balance.

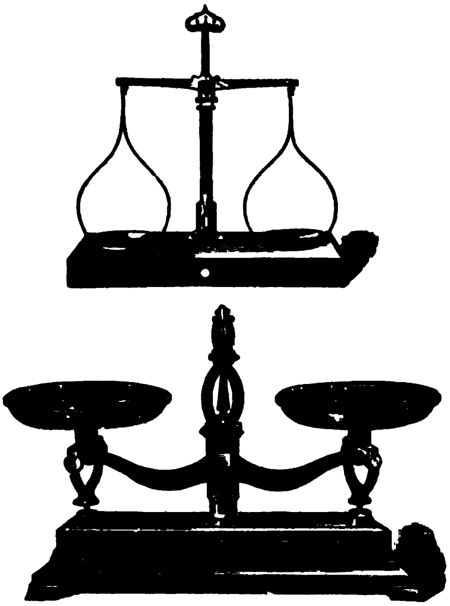

Fig. 15.—Equal-arm balances.

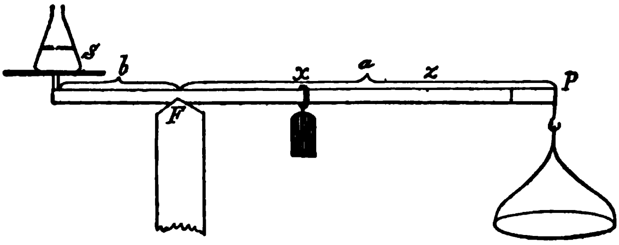

Fig. 16.—Diagram of unequal-arm balance.

The advantage of this arrangement lies in the fact that but one weight is required, the weighing being done by shifting this on the beam. Figure 16 illustrates a scale built on this plan. If the weight *S* is balanced with *W* at *x*, then twice *S* will be balanced at *z*, etc. This principle is also employed in weighing very heavy substances. If the distance *F P* = 10 × *F S*, then each Gm. placed on the pan *P* will indicate 10 Gm. on *S*, etc.

The same principle is used in the *rider* of analytic balances. The arm is here divided into ten parts; a rider of platinum wire weighing 0.01 Gm. can be shifted along this arm, and each division will, of course, indicate $\frac{1}{10}$ of 0.01 Gm = 1 milligram.

Some *mechanical features* in the construction of balances deserve further mention:

The fulcrum consists, in most balances, of a sharp prism of steel or, in better balances, agate,—the so-called *knife-edge*,—supported on a steel or agate rest (Fig. 17). The pans are suspended from similar knife-edges. It is essential that these three edges should be exactly parallel, else the shifting of the position of the weight on the pan will make a difference.

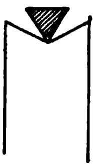

Fig. 17.—Knife-edge.

In the *torsion balance* the fulcrum is formed by a tightly stretched wire firmly fixed to the beam and supporting it. The movements of the latter cause torsion of the wire. This avoids the wearing of the knife-edge.

In the finer balances a *pointer* is attached to the center of the beam to facilitate the observation of its movements. It is not necessary to wait until the pointer comes to rest; balance is secured when it swings to the same extent on each side.

Two screws at the ends of the beam permit of balancing the two arms. Some mechanism exists in all balances for arresting the swing of the beam.

A few words regarding the proper *care of a chemic balance* may be useful.

It should be placed in a perfectly plane position, on a solid table as little liable to vibration as may be obtained. It should be protected against dust by a glass case, against moisture by a jar of $CaCl_2$, and against acid vapors by some Na_2CO_3 placed in the case. The temperature of the room should not be subject to sudden and large alterations. Substances to be weighed should always be placed in containers, such as a beaker or watch-glass, never directly on the scale-pan. The beams should always be put at rest before a weight is changed.

There are *two methods of weighing*: the direct method and the method by substitution.

Direct Weight.—In this, the substance is placed on one pan, and weights added to the other until the two are balanced. The weights employed give the weight of the substance.

Weight by Substitution.—In weighing by substitution a given tare is placed on one scale-pan and counterbalanced by weights. The substance to be weighed is then placed on the side of the weights and weights removed until the two again balance. The difference between the two weighings equals the weight of the substance. This method has the advantage over the former that the beam need not swing perfectly horizontal.

Liquids are weighed by counterbalancing (taring) the empty container, placing the required weight on the other scale-pan, and then adding the liquid until the balance is restored.

8. Measuring is done in graduated vessels, usually of glass ("graduates"). Several points must be kept in mind:

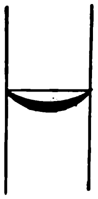

Fig. 18.—Meniscus.

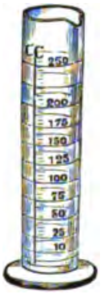

Fig. 19.—Cylindric graduate.

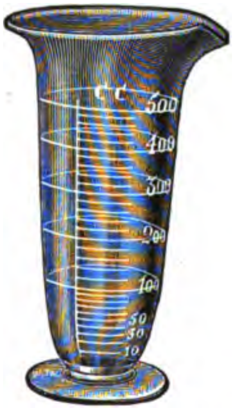

Fig. 20.—Conical graduate.

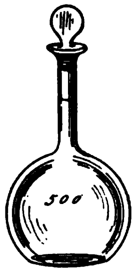

Fig. 21.—Measuring flask.

The vessel containing the liquid must be held so that the level of the liquid is in a perfectly horizontal plane, and at the same height as the eye. This is greatly facilitated by having the marks encircle the graduate. The possibility of error is the greater, the broader the surface.[1] Owing to capillary attraction, the surface of the liquid is always cupped, producing the "meniscus" (Fig. 18). The reading should be taken at the lowest level of the meniscus. *Measuring flasks* and "*graduates*," *i. e.*, the vessels used for measuring larger quantities, are graduated for contents: *i. e.*, the quantity read is the quantity contained in them. Whilst pipettes and burettes are graduated for outflow: the quantity read is the quantity which will flow from them.

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[1] Greater accuracy may therefore be attained if the measuring vessel is as narrow as possible where the reading is taken.

Since the volume of liquids varies with the *temperature*, readings should be made at the temperature for which the measures are adjusted—approximately room temperature. (More exactly, 15° C. = 59° F.)

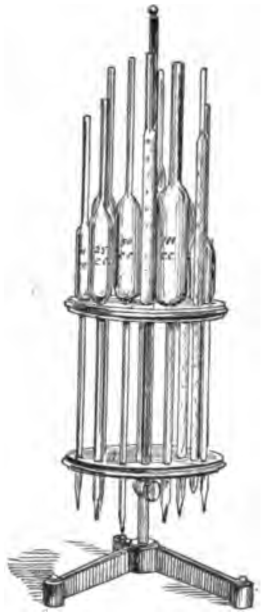

Fig. 22.—Pipettes.

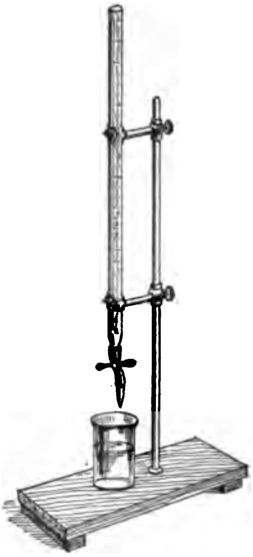

Fig. 23.—Burette.

Graduates are of two shapes, cylindric (Fig. 19) and conical (Fig. 20). Each has its advantages. The former, which is usually employed in scientific laboratories, allows measuring the liquid with equal accuracy at all heights. The conical graduate, on the other hand, allows smaller quantities to be measured with greater accuracy than larger ones, and facilitates cleaning. Measuring flasks are the only accurate method of measuring large quantities of liquids, since the reading part is very greatly constricted (Fig. 21).

For smaller amounts *pipettes* (Fig. 22) and *burettes* (Fig. 23) are employed.

To facilitate the reading of the latter *Erdmann's float* (Fig. 24) is a very convenient aid. The reading is made from the mark on the float. A cheaper way is to use a card with a horizontal line which is adjusted to the lowest part of the meniscus.

A topic closely related to this of metrology is that of

9. Specific Gravity.—This may be defined as the ratio of the weight of a given substance to the weight of an equal volume of a standard. The standard for liquids or solids is (in pharmacy) distilled water at 15° C.[1] (59° F.).

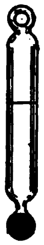

Fig. 24.—Erdmann's float.

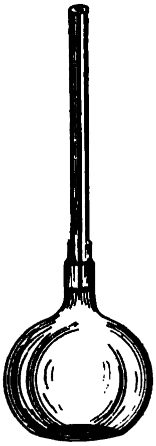

Fig. 25.—Pycnometer.

Methods of Determining Specific Gravity.—

In principle, the weight and volume of the substance must be determined. Since 1 c.c. of the standard (water) weighs 1 Gm., it is only necessary to divide the weight in grams by the volume in c.c. to obtain the specific gravity.

$$\text{Sp. G.} = \frac{\text{W (Gm.)}}{\text{V (c.c.)}}$$

The details must vary with the physical nature of the substance.

I. Liquids.—1. *Pycnometer* (Fig. 25).—A flask whose net weight is known, and also its weight when filled to the mark with water at 15° C., is filled with the liquid whose specific gravity is to be determined, and again weighed.

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[1] In science, distilled water at 4° C. is taken as the standard. It is scarcely necessary to make any correction for ordinary pharmaceutic purposes.

Example:

Weight of pycnometer filled with water = 56.5511
" " " empty = 27.0758
" " water = 29.4753
Weight of pycnometer filled with liquid = 60.2476
" " " = 27.0758
" " liquid = 33.1718
Specific gravity of liquid = 33.1718 ÷ 29.4753 = 1.1254

This is the most accurate method of determining the specific gravity of liquids.

2. By the *loss of weight of a solid.* A body immersed in a liquid loses the weight of its own volume of the liquid. The determination is done most conveniently with a specific gravity balance (Fig. 26).

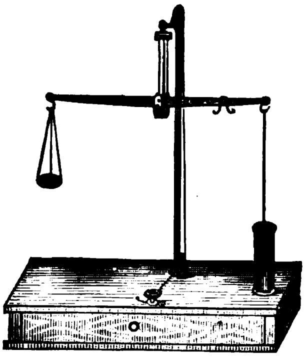
Fig. 26.—Specific gravity balance.

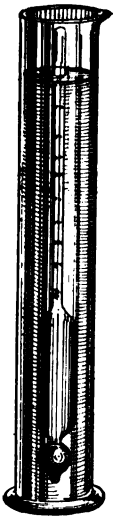
Fig. 27.—Areometer.

Example:

A 50 Gm. weight weighs in distilled water 24.36 Gm.
Loss of weight = 25.64 Gm. = volume of the weight.
The same weight weighs in the liquid 20.15 Gm.
Loss of weight = 29.85 Gm. = weight of equal volume of fluid.
Specific gravity 29.85 ÷ 20.15 = 1.481.

3. *Areometers* (Fig. 27).—These are adjusted to sink in the

liquid to the mark on the stem corresponding to the specific gravity of the liquid. They are not usually very accurate, but are very convenient for ordinary purposes, such as the clinical examination of urine, etc. (urinometer). Formerly they were graduated in artificial scales, but at present they are made so that the specific gravity may be read off directly.

A modification of this method is used for determining the specific gravity of liquids of which only *very small quantities* can be obtained, such as a drop of blood. The blood is drawn directly into a cylinder containing a mixture of benzol (of low specific gravity) and chloroform (of high specific gravity). More of the benzol or of the chloroform is added, according to whether the drop floats on the surface or sinks to the bottom, until it floats about the middle of the liquid without falling or rising. The specific gravity of this mixture is then determined with a urinometer and equals the specific gravity of the blood.

II. Solids.—These are weighed in the usual manner. The method used for the determination of the volume must vary in different cases.

1. Substances insoluble in water:

(*a*) *Displacement of Water.*—The substance is added to a known volume of water and the amount of the latter which has been displaced is measured.

Example:

Weight of substance = 50.5 Gm.

This is dropped into a graduated cylinder containing 50 c.c. of water. The level of the water now stands at 73.2. Amount of water displaced $= \begin{array}{r} 73.2 \\ \underline{50.0} \\ 23.2 \end{array} =$ volume of solid. Specific gravity $= 50.5 \div 23.2 = 2.177$.

With a *solid lighter than water*, this may be submerged by the aid of a wire, and the volume occupied by the latter subtracted.

(*b*) *Loss of Weight in Water.*—Since this is equal to the weight of an equal volume of water, the weight in air divided by the loss of weight in water will be the specific gravity.

Example:

Weight in air	10.52 Gm.	
" " water	8.26 "	
Loss of " " "	2.26 "	volume of solid.

Specific gravity $= 10.52 \div 2.26 = 4.655$.

In case the substance is *lighter than water*, a weight must be attached to it as a sinker, and correction made for this.

Weight of sinker = 20 Gm.
" " " in water = 16 "
Volume of sinker = 20 — 16 = 4 "
Weight of substance = 10 "
" " " + sinker = 30 "
" " " + " in water = 11 "
Volume of substance + sinker = 30 — 11 = 19 c.c.
" " sinker = 4 "
" " substance = 15 "
Specific gravity = 10 ÷ 15 = 0.667.

(*c*) With *powders* the amount of water displaced by a certain weight of the powder is estimated with a pycnometer.

Weight of pycnometer containing some of the dry powder = 20 Gm.
" " " = 15 "
" " dry powder = 5 "

The pycnometer containing the powder is now filled up with water to the mark:

Weight of pycnometer containing powder and water = 42 Gm.
" " " = 15 "
" " powder and water = 27 "
" " " = 5 "
" " water = 22 "
Capacity of pycnometer = 25 Gm.
Amount of water displaced by powder = 25 — 22 = 3 Gm. = volume of powder.
Specific gravity = 5 ÷ 3 = 1.667.

2. If the substance is *soluble in water*, its volume must be determined by substituting some liquid in which it is insoluble for the water in the above methods. The figure so obtained, multiplied by the specific gravity of the liquid used, gives the specific gravity of the solid.

The specific gravity is of use in calculating the *weight or volume of substances:*

To determine the weight of a given volume of a substance, multiply this volume by the specific gravity: weight = volume × specific gravity.

To determine the volume of a given weight, divide the weight by the specific gravity: $\text{volume} = \frac{\text{weight}}{\text{specific gravity}}$

A term which is sometimes used is the "*specific volume*," the volume of a substance compared with the volume of the same weight of the standard. It is the reciprocal of the specific gravity; specific volume $= \frac{1}{\text{specific gravity}}$.

Examples in specific gravity:

1. What is the Sp. G. of a liquid which measures 20 c.c. and weighs 46.5 Gm.?
2. What is the Sp. G. of a liquid which measures 18 c.c. and weighs 14.3 Gm.?
3. What is the Sp. G. of a liquid which measures 1 fl.℥ and weighs 212 gr.?
4. A sinker weighs in the air 7.46 Gm.; in a liquid, 4.25 Gm.; in water, 6.066 Gm. What is the Sp. G. (*a*) of the liquid? (*b*) of the sinker?
5. A sinker weighs in the air 12.46 Gm.; in ether (Sp. G. = 0.725) it weighs 11.15 Gm. What is the specific gravity of the sinker?
6. What is the weight (Troy system) of 1 fl.℥ of (*a*) glycerin (Sp. G. 1.250)? (*b*) olive oil (Sp. G. 0.915)? What is the volume (wine measure) of 1 ℥ Troy of (*c*) chloroform (Sp. G. 1.490)? (*d*) aq. ammonia fort. (Sp. G. 0.901)?
7. What is the specific volume of these four liquids?

CHAPTER III.

PHARMACEUTIC METHODS.

In the making of pharmaceutic products very different methods must be used, depending upon the physical and chemic nature of the crude drug, and upon the character of the desired product.

These may be roughly classified into those used in the making of many different preparations,—*general methods*,—and those used in only a very limited number of cases—*special methods.*

The methods can be best understood when studied in the order in which they are usually applied to the drug. The following table presents the subject in schematic form:

TABLE II.—PHARMACEUTIC PROCESSES.

I. Preparatory:
  - Desiccation.
  - Comminution: Cutting, rasping, grinding, pounding, trituration, levigation.

II. Extraction (Heat Solution, Pressure):
  1. Heat: Distillation, sublimation.
  2. Extraction by solution: Maceration proper (digestion, infusion, decoction), percolation.
  3. Pressure.

III. Other General Pharmaceutic Processes:
  - Requiring heat: Evaporation, torrefaction, carbonization, ignition (incineration or calcination), fusion.
  - Decantation.
  - Expression.
  - Colation.
  - Filtration.
  - Clarification.
  - Dialysis.
  - Solution.
  - Crystallization.
  - Decolorization.
  - Preservation.

IV. Special Processes.

I. PREPARATORY PROCESSES.

Desiccation or Drying.—This is usually the first operation to which the crude drugs are subjected after their collection. It serves a threefold purpose: It reduces the bulk, assists preservation, and facilitates comminution.

Formerly the drying was done by spreading or hanging the drugs in airy lofts. At present they are usually placed on perforated trays in special drying closets and heated artificially (steam, etc.). They are often cut into smaller pieces before this drying. The degree of heat must not be so high as to injure the sometimes very unstable ingredients.

Comminution.—The next step is comminution, or reducing of the substance to smaller pieces.

This is usually done by machinery. Crude vegetable drugs are first sliced or chopped, often before drying. They are then bruised by pounding in a mortar and finally ground, the finer grades of powders often several times, the grinding surfaces being brought closer together each time. The mills for this purpose are constructed on the same general principles as flouring mills, employing stones, rollers, etc. The details of the process used depend upon the physical character of the drug. A fibrous material like licorice root requires a different process from a friable substance like gum acacia.

On the small scale, drug mills, constructed more or less on the principle of the coffee-mill, are used for fibrous, and mortar and pestle for friable drugs. Mortars are made of iron, wedgewood, porcelain, and glass. (Fig. 28.)

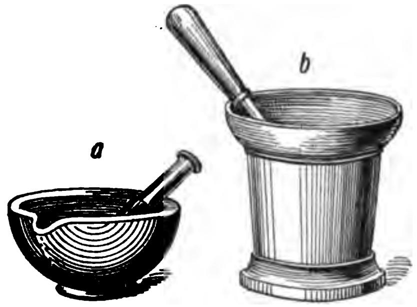

Fig. 28.—Mortars: *a*, Wedgewood or porcelain; *b*, iron.

Trituration is the process of rubbing (not pounding) a substance to a powder in a mortar.

Some points deserve special mention. Often a substance will not powder by itself, but will do so when mixed with another substance—*e. g.*, sugar of milk. This is called "pulverization by intervention." Sometimes it is well to moisten the drug—*e. g.*, camphor with alcohol, nux vomica with steam, etc.

The powders so obtained are classified according to the degrees of fineness. In the process of percolation, presently to be described, it is often essential to use a powder of a certain degree of fineness. The powders are therefore sifted, and are classified according to the size of the meshes of the sieve through which they pass, thus:

No. 80 = 80 meshes to linear inch, very fine.
" 60 = 60 " " " " fine.
" 50 = moderately fine.
" 40 = " coarse.
" 20 = coarse.

Since the different structures in a crude drug do not powder with equal readiness, it is essential that the whole of the drug to be powdered should be passed through the sieve, else the different portions will not have the same composition.

To obtain very fine powders of an insoluble substance, it may be *levigated.*[1] The process of decantation (*elutriation*) is also employed to separate very fine powders, as chalk.

II. PROCESSES OF SEPARATION.

For the separation of the desired ingredients from the inert material three methods are in vogue, depending upon the nature of the active constituents. If volatile constituents are to be separated, this may be readily done by the *application of heat*—distillation and sublimation. If they are fixed, the separation is usually effected by exposing the drug to the *action of some solvent* in which the desired principles are soluble, and the rest, as far as may be, are insoluble. In certain cases some mechanical means are sufficient, as in the separation of fixed oils from seeds, etc., by *pressure.*

Separation by Means of Heat.—This may be done whenever the substances to be separated have a different boiling-point, and are not themselves destroyed by the necessary degree of heat. The methods used must vary according to whether the fixed or the volatile portion is desired, and, if the latter, according to whether it is liquid or solid.

METHODS OF SEPARATION BY HEAT.

Residue desired:
This is Solid: Desiccation, torrefaction, carbonization, ignition.
This is Solid or Liquid: Evaporation.
Vaporized portion desired:
This is Solid: Sublimation.
Liquid: Distillation (simple, fractional or destructive).

Desiccation, Torrefaction, Carbonization, Ignition.—With all these, the object is to drive off some volatile constituent from a solid, the fixed residue being the portion desired.

When the heat employed is of such degree as not to change the chemic composition, the process is spoken of as *desiccation.* This has been partly discussed on page 46.

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[1] Made into a thick paste with water and rubbed between two polished slabs.

For some purposes it is necessary to modify this process. If the last traces of moisture are to be removed, it is necessary to employ heat above that of boiling water, say 110° to 120° C., and the heating must be continued for some time. When such heat is injurious to the substance, the same object may be accomplished by drying in vacuo (p. 51) or by placing the substance in a desiccator (Fig. 29) over some hygroscopic substance—$CaCl_2$, or preferably, concentrated sulphuric acid. A substance or vessel which has been heated and which is to be weighed must always be placed in a desiccator to cool, since moisture is very rapidly attracted from the atmosphere.

Torrefaction.—The process of roasting; the object being to employ such a degree of heat as will alter some of the constituents without affecting others. The roasting of coffee is a familiar example.

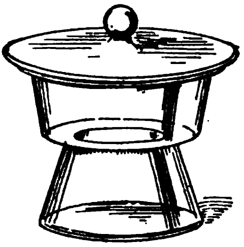

Fig. 29.—Desiccator.

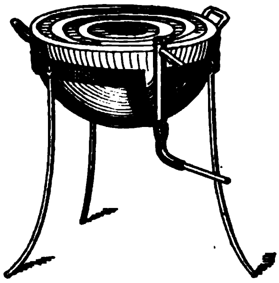

Fig. 30.—Constant level water-bath.

Carbonization.—The heating of organic substances under exclusion of air. The object is to destroy the chemic composition without oxidation; carbon results in the process (vegetable or animal charcoal).

Ignition.—This is the process of strongly heating a substance, usually in a crucible, with full access of air, so as to effect complete oxidation; nothing but the ashes remain.

These methods are discussed in text-books on analytic chemistry.

Evaporation consists in vaporizing the solvent from a solution, the object being the concentration of the dissolved substance.

Since the rapidity of the evaporation, aside from the quantity of heat applied, depends upon the extent of the liquid exposed to the air and to the heat, dishes as flat as possible are chosen.

For ordinary pharmaceutic and chemic purposes, those made of porcelain are of most frequent service. Vessels made of glass, iron, platinum, etc., find application in special cases. The heat may be applied directly, say by means of a Bunsen flame, only a piece of wire gauze or a plate of asbestos or iron being interposed. This method can be used only when there is no danger of injuring the solution by excessive heat, either the substance being incapable of change, or the solvent sufficient in amount so that the temperature cannot rise much beyond its boiling-point. If this is not the case, some method must be used of regulating the amount of heat applied, and this is done by applying the heat indirectly through a bath. This consists of an outer vessel filled with water (steam), oil, sand, or air.

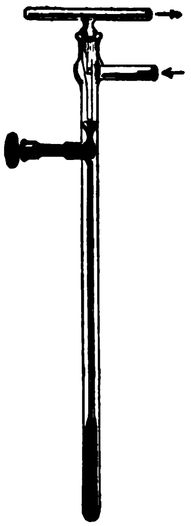

Fig. 31.—Thermo-regulator.

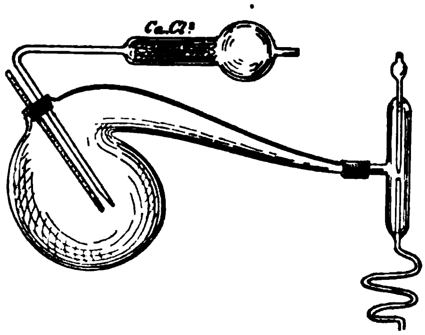

Fig. 32.—Apparatus for evaporation in a vacuum with current of dry air.

The water and oil baths can, of course, be used only for temperatures below the boiling-point of these liquids. This is rather higher for oils, but these possess the disadvantage that irritating vapors arise from them. On the other hand, oil does not evaporate as does water. Water-baths require constant attention to prevent them from drying. Constant level water-baths have been devised to obviate this difficulty. They are constructed either on the principle of Mariotte's bottle, or by passing a continuous stream of water through the outer vessels. (Fig. 30.)

Steam is sometimes used instead of water.

Air- and sand-baths are capable of regulation at any temperature. The latter, however, are frequently used merely for the purpose of moderating and equalizing the heat. Air-baths may be improvised by covering a tin pan with a sheet of iron. A much better method is by means of an oven, which may be covered with asbestos.

For keeping the temperatures of air and water ovens constant, various thermoregulators are used of which figure 31 is an example.

The rapidity of evaporation may be considerably increased by *stirring*, thus exposing a constantly renewed surface to the air. The same object may be secured by creating a current after the manner of a smokestack, by supporting an *inverted funnel* over the evaporating dish.

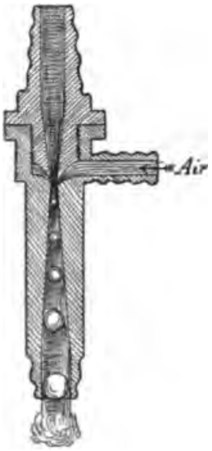

Fig. 33.—Principle of filter-pump.

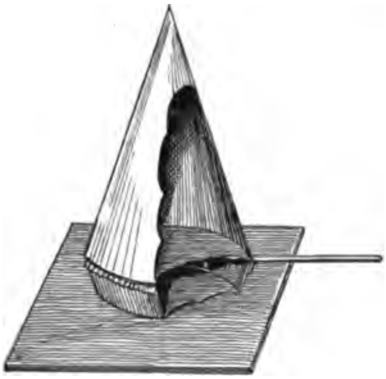

Fig. 34.—Sublimation of benzoic acid (Coblentz).

In cases where the evaporation must be carried on at a temperature below the boiling-point of the solvent, this may be done either by evaporation over H_2SO_4, or in a vacuum, or by passing a current of dried air through the liquid. Figure 32 shows an apparatus for the evaporation of liquid at low temperature, combining vacuum and fine stream of dried air. The tube which carries the air must have a fine capillary opening. Figure 33 shows the principle of the ordinary water filter-pump used to produce the vacuum.

The evaporation which occurs from the surface of a liquid exposed to air at ordinary temperature is called "*surface evapo-*

ration." It varies in quantity with the amount of surface exposed and with the temperature and dryness of the air.

When very inflammable liquids (ether) are being evaporated, this should be done on a large water-bath, and the Bunsen flame should be protected by wire gauze.

Sublimation.—The process of separating a volatile from a non-volatile solid.

(The difference between sublimation and distillation consists in this, that the product is solid in the former, liquid in the latter.)

This may be done in a distilling apparatus, provided that the cooling tube has sufficient lumen to prevent its clogging by the condensation of the sublimate. The apparatus is, however, usually modified. A simple illustration of this process is the old method of manufacturing benzoic acid from gum benzoin, a paper hood being used as condenser. (Fig. 34.)

Distillation.[1]—The typical apparatus used for distillation consists of three parts (Figs. 35 and 36):

The *still*, the vessel in which the vapor is generated.

The *condenser*, the apparatus in which the vapor is cooled.

The *receiver*, for receiving the condensed product.

The Still.—This consists of either a retort, an alembic, or a flask.

The *retort* is illustrated in figure 37. The bend at *X* should go as far as possible inward, so as to prevent the carrying over of liquid. In filling a retort, care must be used not to get any liquid in the neck. A funnel with a long tube attached must therefore be used. An opening (tubulure) at *a* is convenient for filling and for holding a thermometer.

The *alembic* is the old-time still, and differs from the retort in having a chamber (helm or hood) where the vapor is partly condensed. By fitting the helm on the body with a flange joint a very wide opening can be secured, which is of use in cleaning.

Flasks with perforated corks answer for most purposes. The cork should contain two holes, to allow the introduction of a thermometer. To prevent the projection of liquid into the delivery tube during too violent boiling, the upright limb can be expanded into a bulb.

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[1] Although this is such a ready and simple means of separation that one would think that it must have been discovered at a very early time, such does not appear to have been the case. We find the first record of it in the writings of the fourth century alchemists.

Liquids in contact with very smooth surfaces—*i. e.*, in glass vessels—may be heated to a temperature considerably above their "boiling-point," when the vapor is suddenly disengaged, and causes "*bumping.*" This may be avoided by introducing some irregular bodies into the flask—glass, zinc, pumicestone, platinum wire, etc., according to the nature of the liquid.

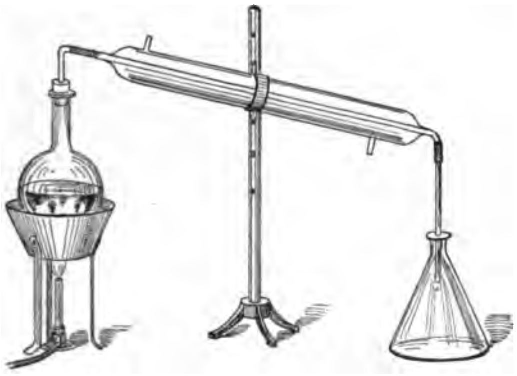

Fig. 35 —Still, Liebig's condenser, and receiver.

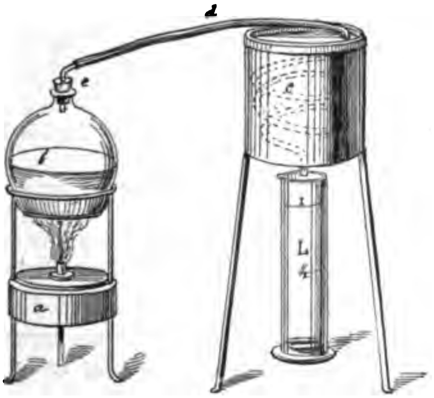

Fig. 36.—Still, worm condenser, and receiver.

The Condenser.—The object of this apparatus is to cool and consequently condense the vapors which have been formed in the heated still.

With substances having a very high boiling-point, above 150° C., the air alone may be sufficient to effect condensation. With most substances, however, a constantly renewed layer of cold water is necessary.

The form of condenser which is most used in laboratories on account of its convenience is the *Liebig's* (Fig. 35).

The *worm* offers a larger surface (Fig. 36).

As *receiver*, a common flask or beaker is ordinarily used.[1]

The heating of the retort may be done in any of the ways mentioned under evaporation. With substances which are injured by being heated alone, the distillation is done by a current of steam generated in another vessel.

Fractional distillation is the process of separating a mixture of liquids of different boiling-points by distillation.

This cannot be done with any degree of completeness unless the boiling-points lie far apart. The separation, however, will be the more complete, the more exactly the temperature can be observed and controlled. The thermometer-bulb must be adjusted at the level where the vapors leave the flask. This is facilitated by using "fractional distillation flasks" (Fig. 38).

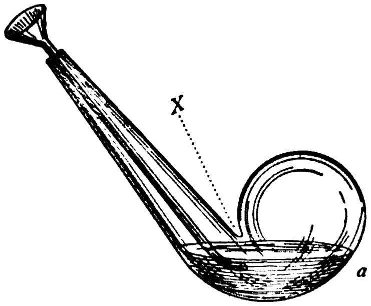

Fig. 37.—Filling a retort.

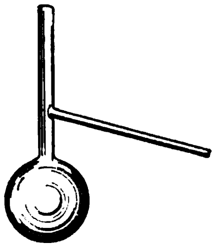

Fig. 38.—Fractional distillation flask.

Destructive distillation is the name applied to the process of heating a substance so strongly as to decompose it, and collecting the volatile products arising from this decomposition : *i. e.*, in the case of organic bodies, tar.

This is ordinarily done in iron retorts.

Solution.—This consists of incorporating a solid into a liquid in a state of "molecular subdivision."

That is, the molecules of the solid diffuse themselves in the liquid and become so widely separated that no solid particles are

[1] It would be without the scope of this treatise to enter into the method of glass-blowing, cork-boring, etc., which are needed in fitting up a still. Such will be found in most elementary text-books on chemistry.

by any means discernible. In other words, the solid is liquefied and its molecules intermingle with those of the solvent.

A *simple solution* is one occurring in the manner described, the change in the solid being physical. When a chemic change takes place, the process is called *chemic solution* (such as the solution of a metal in an acid).

A solvent is capable, under given conditions, of dissolving but a limited amount of a given solid. A solution which contains as much of the solid as the liquid can dissolve under these conditions is called a *saturated solution*. The condition which has the greatest influence upon solubility is the temperature. A liquid can usually dissolve the more of the solid, the higher the temperature. There are, however, a few exceptions to this rule.

If a solution saturated at a high temperature is allowed to cool, the originally dissolved substance will be in excess of saturation. Under certain conditions it may still remain in solution at the lower temperature, this being a *supersaturated solution*. Ordinarily, however, the excess will separate, usually in crystalline form. This process is called *crystallization*. It is frequently used as a means of purification.

A solution which contains less of the solid than it is capable of dissolving is an unsaturated solution. A solution which is saturated with one substance is still capable of dissolving others, though not as much as if it were the pure solvent.

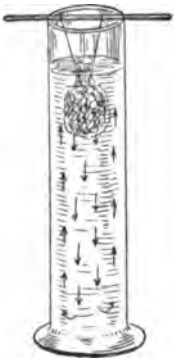

Fig. 39.—Circulatory solution.

Solution is effected by placing the solvent in contact with the substance to be dissolved. The process may be hastened by applying heat, or by exposing the largest possible surface to the action of the solvent. The latter may be done by using the substance in a pulverized condition, and by constant stirring. With *circulatory solution* the substance is suspended near the surface of the solvent. As this takes up the substance, it gains in specific gravity, and hence sinks to the bottom, a new portion of liquid taking its place. (Fig. 39.) The same object may be secured by a process analogous to percolation, the powder being placed in a funnel partly occluded by a pledget of cotton, etc., and the solvent allowed to percolate through it.

The simple solution of a substance always causes a depression of temperature. But if a chemic change occurs, the temperature may be raised.

The process of solution applied to crude drugs has for its purpose the separation of the active ingredients from the insoluble inert material. The object is to dissolve out the greatest possible amount with the least possible menstruum. This accomplishes two results: We obtain a strong extract, and we waste neither drug nor menstruum. There are a number of methods of accomplishing this, each with its advocates. They are combinations of two extremes: maceration and percolation. Neither of these is commonly used alone in this country, the practice being to combine the two.

Maceration is by far the simpler process. It consists in simply leaving the solvent in contact with the drug under suitable conditions for a sufficient length of time.

When maceration alone is employed, a given quantity of the drug is put in a bottle or other suitable vessel with a definite proportion of the solvent (called menstruum) and left a certain time, usually two weeks. The liquid is then strained off, the residue (marc) is expressed and the mixed extract filtered. The details of the process are influenced by several considerations:

(*a*) The degree of comminution of the drug: The finer the drug, the less time will be required, and sometimes it is impossible to get thorough penetration unless the drug is powdered. A coarse powder gives a cleaner solution.

(*b*) Temperature: The solution is the quicker, the higher the temperature. Different names are given to the process according to the temperature at which it is carried out. Maceration proper = room temperature; 30° to 40° C. = digestion; boiling = decoction. Possible injury to some constituents by heat, or evaporation of a constituent or of the solvent, are objections to the application of heat in certain cases.

(*c*) Time: the longer the better.

(*d*) Menstruum. This must be adapted to the drug. Resins, oils, etc., require other solvents than do gums, etc. (See p. 59.) A combination of solvents may sometimes be used.

This process of maceration is the one almost exclusively employed in Europe; and it offers certain advantages, not the least being its simplicity and the constant results which it gives. Its main disadvantages are the required time and the loss of the extract retained in the insoluble residue or "*marc.*" Certain drugs are physically unfit for percolation, since the moistening causes them to form into a tough mass, as good as impenetrable to the solvent.

The loss of menstruum does not, of course, weigh when an aqueous solvent is used and only small quantities are prepared. Hence maceration is used in making infusions and decoctions.

Infusions are made by pouring boiling water upon the drug (in coarse powder), letting it stand for half an hour, and straining. The usual proportion is 1 : 20. In *decoctions*, the drug is boiled for a quarter of an hour in a covered vessel with water (1 : 20), allowed to cool, strained, and diluted to 20. These preparations do not keep. To secure preservation, acetic acid, glycerin, sugar, or, most commonly, alcohol is added.[1]

Percolation consists in passing a solvent through a thick layer of the powder to be exhausted. This exposes a large surface of the latter; the nearly saturated solvent flows off and fresh unsaturated portions continuously replace it, insuring very rapid solution.[2]

The principle of the method is to pack the powder into a tall vessel, with an opening at the bottom, and to let the solvent trickle through it. Usually the process is combined with a short previous maceration.

The details are as follows:

The powder (the fineness of which depends upon the nature of the drug and is directed for each case by the Pharmacopœia) is moistened in a jar with some of the menstruum. This moistening is for the purpose of swelling the drug, for if this took place in the percolator, the drug would become so firmly impacted that the menstruum could not penetrate through it; or it could even burst the percolator.

The choice of the shape of the percolator depends upon the nature of the drug. Should the drugs have a tendency to swell, particularly if they are in fine powder or if weak alcohol menstruum is used, a conical percolator is employed; otherwise, the cylindrical. The size corresponds to the quantity of the powder.

The percolator is prepared in the following manner (Fig. 40): Into the small end there is inserted a cork perforated by a short glass tube which projects about 1 cm. inside the percolator. The outer end of this tube is attached to a piece of rubber tubing, about one-fourth longer than the percolator, and this to a U-shaped glass tube. This is held to the percolator by a rubber band in such a way that it can be raised and lowered. The percolator is then set in the stand. A pledget of absorbent cotton is loosely packed in the neck of the percolator, and this is covered by a layer of clean sand, and over this goes a well-fitting disk of filter-paper. Then the moistened drug is pressed in—and this is the part of the process which requires the greatest skill and judgment, and on it depends the success of the product. It should be done very evenly, else the menstruum will choose the path of least resistance and some portions of the powder will be entirely exhausted whilst others are still scarcely affected. The firmness of the packing is also of great importance: if not firm enough, the menstruum will run through too rapidly and the percolate will consequently be weak. If too firm, it can not run at all; and if any swelling occurs, the percolator will be broken. Drugs in coarse powder should be packed more firmly than fine powders. An alcoholic menstruum requires firmer packing than a watery one. Beyond these, very few rules can be given, experience being in many cases the only guide.

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[1] The amount of preservative which must be added to a preparation to insure its keeping qualities, must vary with its nature, and in the same direction as the amount of "extractive." The proportions generally necessary are: Alcohol, 20 to 25%; glycerin, 10%; sugar, 66 Gm. to 100 c.c. of finished product. Alcohol 20% + glycerin 5%.

[2] The U. S. Pharmacopœia defines percolation as consisting in "subjecting a substance or a mixture of substances, in powder, contained in a vessel called a percolator, to the solvent action of successive portions of a certain menstruum, in such a manner that the liquid, as it traverses the powder in its descent to the receiver, shall be charged with the soluble portion of it, and pass from the percolator free from insoluble matter."

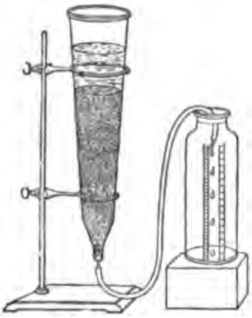

Fig. 40.—Method of percolation (Thornton).

The packing being completed, the menstruum is poured on until it stands an inch or two above the drug; the percolator is then covered and set aside for maceration for a specified time, the tube being raised so that no liquid flows out. When the time of maceration is completed, the tube is lowered and fixed at such a level that the outflow occurs at the rate of 10 to 30 drops per minute. New menstruum is poured on in the measure that the old flows out. Care should be taken to always maintain the layer of liquid above the powder; else cracks may appear in the latter, necessitating repacking.

The process is continued, in the case of tinctures, until a certain volume of percolate is obtained. The quality of the percolate will, of course, depend upon the care and skill of the operator, and the product is apt to vary. Maceration would, therefore, be a better process for tinctures.

This difficulty is avoided in the case of extracts, for here the percolation is continued "until the drug is exhausted"; *i. e.*, until the active ingredients have become completely dissolved out. This is recognized by testing the last portions of the percolate in the appropriate manner, such as Meyer's reagent for alkaloids, water for resins, etc. It may here be remarked that a drug is usually more rapidly exhausted of its active ingredients than of its coloring-matter, so that the last portions of percolate may be colored and yet devoid of activity.

The choice of a menstruum must be determined by the nature of the constituents. The object is, to extract all the active ingredients and the minimum of inactive. Alkaloids and resins require strong alcohol; gums, weak alcohol; licorice, alkaline alcohol; sanguinaria and ergot, acidified alcohol; gentian and quassia, water plus alcohol enough to keep.

In the case of *very volatile menstrua*, such as ether, chloroform, or petroleum ether, some means must be employed to collect and return the evaporated solvent. One of the best apparatus of this kind is that of Soxhlet (Fig. 41). The powder to be extracted is placed in a cartridge of filter-paper (*A*) and this is inserted into the large tube (*a*). The ball condenser *B* and the flask *e*, the latter filled about one-half with the menstruum, are then connected by well-fitting cork stoppers, and the flask set in a heated water-bath. As the solvent is vaporized the vapors go through *c* and reach the outer space of the ball condenser. Here they come in contact with the large surface of the inner ball, through which cold water is passing. They are condensed, and the drops so formed fall on the drug in *a*. As soon as the liquid in this reaches the upper level of the siphon *b*, this is put into action, and the liquid all runs into the flask *e*, when the cycle is repeated.

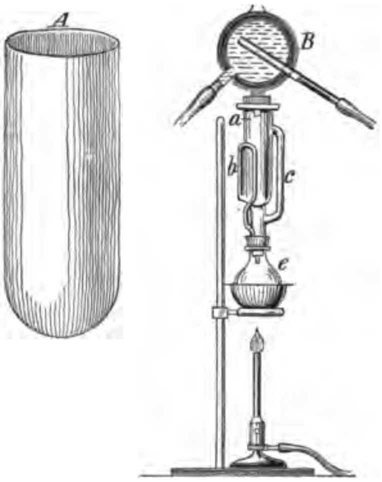

Fig. 41.—Soxhlet extractor (see text).

Expression.—The process of separating a liquid from a solid by pressure.

Its principal employment in pharmacy is for the recovery of tinctures from the "marc"; *i. e.*, the liquid retained by the drug residue after maceration and percolation. It is also a process of separating fixed oils.

The drug is put in a coarse strong cloth and subjected to pressure in a press. These are of various patterns: screw, lever, hydraulic, or centrifugal. The pressure must be applied gradually to prevent the bursting of the cloth. Small quantities can often be pressed sufficiently by putting them into a cloth and tightly twisting the end.

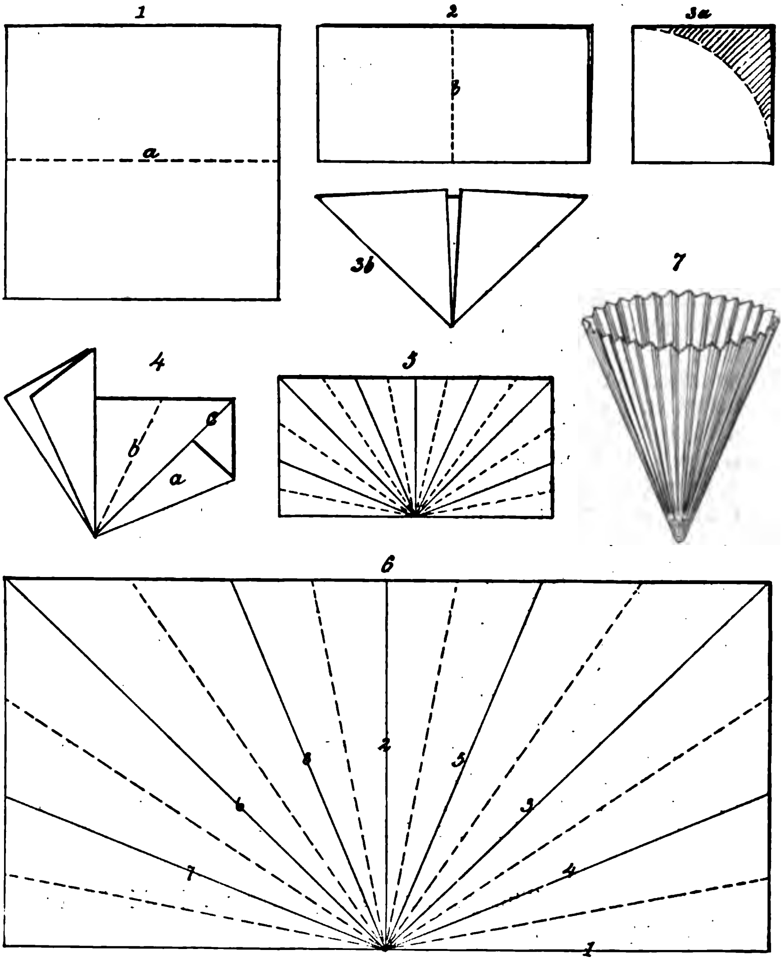

Fig. 42.—Methods of folding filters.

Straining or **Colation.**—The process of separating solid coarse particles from a liquid by pouring it through a cloth or strainer.

Filtration.—The process of separating solid particles (fine or coarse) from a liquid by pouring it through a finely porous material, such as filter-paper.

The usual material for filtration is pure unsized paper, "filter-paper," which is made of various grades,—white and gray,—and of varying texture and thickness according to the purpose for which it is to be used.

There are two principal methods of folding a filter—plain and plaited (Fig. 42).

The former is made by folding a square or round sheet of filter-paper along the line 1, *a*; and this piece again in the same way along 2, *b*. If square, the corner is trimmed off along the dotted line 3, *a*. The filter is then placed in the funnel, opened, and moistened with water or a little of the liquid to be filtered.

The plaited filter is started like the plain. The fold 1, *a* is made; 2, *b* is here only a crease. The paper is flattened again as in 2, and the edges folded in as in 3, *b*. The paper is again laid out flat and each eighth furnished with an extra crease, as in 4; first as in *a*, then folding over *c*, and then making *b*. The paper, flattened out, shows creases as the lines in 5, all in the same direction. Each space is now folded back along the dotted line in the opposite direction, as in making a fan (6). The numbers in (6) refer to the order in which the creases are made. If this is separated, it gives the figure 7.

These two filters have different uses. The plaited filter offers a much larger surface for filtration and is therefore more rapid; it is the form usually employed in pharmacy. The plain filter, on the other hand, facilitates washing and removal of the precipitate, and is of more frequent use in chemistry.

Several points deserve special notice:

The creases should not be carried sharply to the point, but should be quite light ¼ to ½ inch from the end, to prevent breaking.

The liquid should be poured in cautiously, so as to fall about the outer third of the surface of the liquid: if poured at the center, the momentum is apt to break the point of the filter; if poured too near the edge, it is apt to get outside.

Filtration may often be hastened by the use of a vacuum apparatus. (Fig. 33, p. 51.)

Other materials are sometimes employed instead of paper. A very useful filter for large quantities of liquid is made from felt. A plug of glass-wool or asbestos placed in the tube of the funnel is especially useful for strong acids or alkalies. A cell of porous clay is also employed, as in the various forms of the Chamberland filter. With this a vacuum is indispensable.

Another process of frequent use in the separation of crystalloids from colloids is *dialysis.*

When water is added to an aqueous solution of any substance, the dissolved molecules will tend to distribute themselves evenly throughout the liquid. This diffusion will occur, in the case of crystalloids, even when the solution is separated from the water by a parchment membrane. In other words, the crystalloid molecules pass freely through the pores of the membrane under the given conditions. Colloids, such as proteids, gums, gelatin, etc., on the other hand, do not pass through, so that this gives a method for separating these two classes of substances. The most useful form of dialyzer is furnished by a parchment tube containing the solution and suspended in a vessel of water.

Decolorization.—It is often desirable to remove the coloring-matter from a solution. This may sometimes be accomplished by choosing appropriate solvents. More often, however, the solution is filtered through recently calcined animal charcoal. This very often retains some of the active constituents as well as the coloring-matter.

CHAPTER IV.

(A) SPECIAL PHARMACEUTIC PREPARATIONS.

THE Pharmacopœia divides its preparations into certain definite classes, established by long usage, such as Waters, Spirits, Tinctures, Extracts, Pills, Plasters, Ointments, etc. This classification will be retained. The classes will be discussed as regards their definition; reason of existence; some general notion of the manner of preparation; the strength of their more important members.

For convenience of study, it is customary to combine these classes into larger groups. In doing so we shall not bind ourselves to any definite or arbitrary scheme, but shall use now one, now another character, as they may seem important.

Groups of Pharmaceutic Preparations:

A, Liquids; *B*, Solids. Liquids again into *I*, Solutions; *II*, Mixtures. Solutions into 1, Solutions proper; 2, Extracts.

A further subdivision is effected by the nature of the solvent; aqueous, alcoholic, or other.

TABLE III.—SCHEMA OF SOLUTIONS AND EXTRACTS.

1. SOLUTIONS PROPER.—	(*a*) *Aqueous:*	Aquæ. Liquores. Mucilagines.	
	(*b*) *Alcoholic:*	Spiritus.	
	(*c*) *Other menstrua:*	Glycerita (Glycerina, B.P.). Oleata. Collodia.	
2. EXTRACTS (solid as well as liquid).—	(*a*) *Aqueous:*	Infusa. Decocta.	
	(*b*) *Alcoholic:*	Tincturæ. Succi. Liquores concentrati (B. P.). Extracta fluida (liquida, B. P.). Extracta. Abstracta. Resina.	
	(*c*) *Other menstrua:*	Syrupi. Elixiria. Mellita. Oxymellita (B. P.). Confectiones (solid).	(Saccharine.)
	Here may be inserted:	Aceta (vinegar). Oleoresina (ether).	

TABLE IV.—SOLVENTS USED IN PHARMACY (U.S.P.).

Alcohol. 91% by weight, 94% by volume. Sp. G. 0.820.

Alcohol dilutum. 41% by weight, 49% by volume; made by mixing equal parts of alcohol and water.

Alcohol dissolves: Volatile oils, resins, alkaloidal salts, glucosids.

Precipitates: Gums.

Ether. 96%. Sp. G. 0.750.

Dissolves volatile and fixed oils, fats, resins, glucosids, free alkaloids.

Chloroformum. 99%. Sp. G. 1.490.

Solvent properties nearly the same as ether.

Petroleum Ether. The portion of petroleum distilling below 40° C.

Dissolves the same as ether, with the exception of resins, which are insoluble in it.

Glycerin. 95%. Sp. G. 1.250.

Dissolves gums, salts, sugar, alkaloidal salts.

Aqua Destillata. Dissolves salts, gums, and alkaloidal salts, acids and alkalies, etc.

WATERY SOLUTIONS.

Their advantage lies in the fact that water is a cheap solvent of very wide applicability, itself devoid of any therapeutic property. In the case of substances which are insoluble in it, it cannot of course be employed. The greatest drawback lies in the fact that watery solutions of organic substances do not keep. If the quantity of organic matter is small, fungoid growths develop; if large and proteids are present, infusoria are also frequent. Solutions of chemic substances are less subject to this change, as they do not furnish a pabulum, and are often themselves antiseptic.

1. **Aquæ** (*Waters*).—Clear aqueous solutions of volatile substances. Two very dissimilar classes of preparations come under this heading:

(*a*) Extremely weak but saturated solutions of almost insoluble organic substances, for the most part essential oils. These are alone included under Aquæ in the B. P.

The quantity of active substance in them is just large enough to give them a pleasant flavor without imparting to them any noticeable therapeutic properties. The absence of alcohol makes them good solvents for salts, which are generally insoluble in this liquid. Hence their main use is as a pleasant vehicle (a vehicle being the substance which serves for the conveyance of another substance). Dose practically ad libitum.

(*b*) Solutions of chemic gases. Strong and with distinct therapeutic properties. Their dose is usually a few drops. (In the British Pharmacopœia these come under the heading of Liquores.)

Preparation of first class: These are prepared either by distillation or by trituration; Aq. Creosoti and Chloroformi by shaking.

In the method of trituration, the object is to distribute the oil as finely as possible, by the intervention of some inert and insoluble foreign substance, so as to facilitate solution. Various methods have been employed for this purpose. The process now official is one of the best.

Example:

Aqua Menthæ Piperitæ (U.S.P.).—Triturate 2 c.c. of oil of peppermint with 4 Gm. of precipitated calcium phosphate until thoroughly distributed; then add gradually 1000 c.c. of distilled water, under constant trituration, and filter.

Waters, as a rule, do not keep well. Their keeping qualities may be improved by adding to them some of the oil of which they are solutions. This floats on the surface, and in this way excludes air and bacteria, and at the same time insures permanent saturation.

Preparation of second class: The second class is prepared by passing the gas through water. The quantity of dissolved gas is then tested by chemic assaying and the solution standardized.

Examples:

Aq. Chlori: Cl developed by action of HCl on MnO_2:

$$MnO_2 + 4HCl = MnCl_2 + 2H_2O + 2Cl.$$

Decomposes rapidly:

$$2Cl + H_2O = 2HCl + O.$$

Aq. Hydrogeni Peroxidi:

$$BaO_2 + H_3PO_4 = BaHPO_4 + H_2O_2.$$

2. Liquores.—Aqueous solutions of solid chemic salts or hydrates, made either by directly dissolving the pure salt in water by trituration or heat; or, more often, by chemic decomposition (simple and chemic solution). (The British Pharmacopœia includes solution of gases and alcoholic solution of fixed substances under this heading.)

They often have ***antiquated names:***

Spirit. Mindererus = Liquor Ammonii Acetatis.
Donovan's Solution = " Arsenii et Hydrargyri Iodidi.
Lugol's Solution = " Iodi Compositus.
Lead Water = " Plumbi Subacetatis.
Goulard's Extract = " " " Dilutus.
Water Glass = " Sodii Silicatis.
Basham's Mixture = " Ferri et Ammonii Acetatis.
Monsel's Solution = " Ferri Subsulphatis.
Effervescent Magnesia = " Magnesii Citratis.
Fowler's Solution = " Potassii Arsenitis.
Labarraque's Solution = " Sodæ Chloratæ.

Their use consists mainly in the convenience of measuring the relatively large volumes of the solution against weighing the small quantity of salt. Water is chosen as the solvent because salts are but little soluble in alcohol, and because the therapeutic qualities of the latter are not desired.

Solutions, when used for special purposes, receive special names, thus: Injectiones (Hypodermicæ; Urethrales), Collyria (Eye-waters), Lotiones (Washes), Gargarisma (Gargle), etc.

The **preparation** of typical chemic solutions is well illustrated on iron, by the aid of the following equations:

Liq. Ferri Chlor.:

(1) $Fe + 2HCl = FeCl_2 + 2H$.
(2) $6FeCl_2 + 6HCl + 2HNO_3 = 3Fe_2Cl_6 + 4H_2O + N_2O_2$.

Liq. Ferri Tersulph.:

(3) $6FeSO_4 + 3H_2SO_4 + 2HNO_3 =$
(4) $3Fe_2(SO_4)_3 + N_2O_2 + 4H_2O$.

From this are prepared Liq. Ferri Acet., Citr., Nitr.; and Ferri et Amm. Acet. after this model:

(*Liq. Ferri Citratis.*)

(5) $Fe_2(SO_4)_3 + 6NH_3 + 6H_2O = Fe_2(OH)_6 + 3(NH_4)_2SO_4$.
(6) $Fe_2(OH)_6 + 2(H_3C_6H_5O_7) = Fe_2(C_6H_5O_7)_2 + 6H_2O$.

One may easily calculate by stœchiometric calculation how much of each constituent will be required.

Question 1: How much Aq. Ammon. will be required to transform the $Fe_2(SO_4)_3$ contained in 100 Gm. of Liq. Ferri Tersulph. into Ferric Hydrate?

100 Gm. Liq. Ferri Tersulph. = 28.7 Gm. $Fe_2(SO_4)_3$ (Mol. Wt. = 399.2).
1 mol. $Fe_2(SO_4)_3$, according to equation (5), requires 6 mol. NH_3 (Mol.
399.2 " require $6 \times 17 = 102$ NH_3. [Wt. = 17).
28.7 Gm. " " $102 \times \frac{28.7}{399.2} = 7.31$ Gm. NH_3.

Aq. Ammon. = 10% NH_3 ∴ 100 Gm. Liq. Ferri Tersulph. requires 73.10 Gm. Aq. Ammon.

Ans.: 73.1 Gm.

Question 2: How much $Fe_2(OH)_6$ will this give?

1 mol. $Fe_2(SO_4)_3$ (399.2), according to equation (5), gives 1 mol. $Fe_2(OH)_6$ [(213).
28.7 Gm. " give $213 \times \frac{28.7}{399.2} =$ *15.6 Gm.* $Fe_2(OH)_6$ = [*Answer.*

Question 3: How much Citric Acid will be required to transform 15.6 Gm. $Fe_2(OH)_6$ into $Fe_2(C_6H_5O_7)_2$?

1 mol. $Fe_2(OH)_6$, according to equation (6), requires 2 mol. $H_3C_6H_5O_7$.
213 " require 383 $H_3C_6H_5O_7$. [(191.5).
Hence 15.6 " " $383 \times \frac{15.6}{213} =$ *27.1 Gm.* $H_3C_6H_5O_7$ = *Answer.*

Question 4: How much $Fe_2(C_6H_5O_7)_2$ will this give?

1 mol. $Fe_2(OH)_6$, according to equation (6), gives 1 mol. $Fe_2(C_6H_5O_7)_2$.
213 " give 498.8 $Fe_2(C_6H_5O_7)_2$. [(498.8).
Hence 15.6 " " $498.8 \; \frac{15.6}{213} =$ *36.5* $Fe_2(C_6H_5O_7)_2$ = *Answer.*

Other chemic solutions are prepared according to the following equations:

Liq. Ferri Subsulphatis:

Probably: $4FeSO_4 + H_2SO_4 + 2HNO_3 = Fe_4O(SO_4)_5 + N_2O_2 + H_2$.

Liq. Hydrarg. Nitratis:

$$HgO + 2HNO_3 = Hg(NO_3)_2 + H_2O.$$

Liq. Plumbi Subacet.:

$$Pb(C_2H_3O_2)_2 + PbO = Pb_2O(C_2H_3O_2)_2.$$

Liq. Ammon. Acetatis:

$$NH_4HCO_3.NH_4NH_2CO_2 + 3HC_2H_3O_2 = 3NH_4.C_2H_3O_2 + H_2O + 2CO_2.$$

(If this is prescribed with alkaloids more acid should be added.)

Strength of the Most Important Liquors.

		In Both Pharmacopœias.	U.S.P.	B.P.
	All liquors containing arsenic	1% As salt.	. . .	. . .
U.S.P.	Liq. Ferri Chloridi	. . .	37.8% Fe_2Cl_6	. . .
B.P.	Liquor Ferri Perchloridi . . .	. . .	. . .	6% Fe.
B.P.	Liquor Ferri Perchloridi Fortis	. . .	. .	22½% Fe.
U.S.P.	Liquor Iodi Compositus . . .	. . .	5% I	. . .
B.P.	Liquor Iodi Fortis	. . .	. . .	14% I.
	Liq. Plumbi Subacetatis [Fortis, B.P.]	25%	. . .	. . .
	Liq. Plumbi Subacetatis Dilutus	. . .	¾%	⅓%
	Liquor Potassæ or Sodæ . . .	5%	. . .	. . .
B.P.	Liquor Atropinæ Sulphatis, . .	. . .	. . .	1%
B.P.	Liquor Morphinæ Acetatis . . .	. . .	. . .	
B.P.	Liquor Morphinæ Hydrochloratis	. . .	. . .	
B.P.	Liq. Strychninæ Hydrochloratis	. . .	. . .	

Injectiones Hypodermicæ (B.P.) are strong watery solutions of active drugs, intended for subcutaneous administration. They are sometimes preserved sterile by the addition of carbolic or salicylic acid. *Dose*, 2 to 10 min. (B.P.).

The following are official (B.P.):

Injectio Apomorphinæ Hypodermica, 1%.
Injectio Cocainæ Hypodermica, 10%.
Injectio Ergotæ Hyp., 30% of extract.
Injectio Morphinæ Hyp., 5% of extract.

3. **Mucilagines.**—Aqueous solutions of gummy substances.

Since gums are insoluble in alcohol, mucilages are incompatible with this substance. They should be recently prepared because they are very apt to mold. They are prepared by either hot or cold process: the former being solution by heat, the latter by percolation. The former should be used only when necessary (tragacanth), as heat usually causes discoloration of the product.

ALCOHOLIC SOLUTIONS.

Alcohol is a specific solvent of certain substances (volatile oils, alkaloids, resins). In prescribing, avoid mixing these with an aqueous solution.

Further, alcohol is a good preservative; but it has distinct therapeutic qualities, which may or may not be useful.

4. **Spirits.**—Alcoholic solutions of volatile drugs. They are all fairly strong.

As in Aquæ we have, as to **preparation**: *Simple solution; distillation* (liqueurs and strong "liquors"); *chemic decomposition* (spiritus æther. nitrosi).

Spirit. Æther. Nitrosi: Ethyl nitrite is prepared by acting on alcohol with nitrous acid.

$$NaNO_2 + H_2SO_4 = NaHSO_4 + HNO_2.$$
$$HNO_2 + C_2H_5HO = C_2H_5NO_2 + H_2O.$$

This is distilled and purified by washing with water and sodium carbonate and dissolved in alcohol.

Strength of Spirits:

Spiritus Ammoniæ, 10%.
" " Arom. contains about 1% NH_3.
" Camphoræ, 10%.
" Glonoini, 1%.
" Phosphori, 0.12%.
" Æther. nitros., 4% $C_2H_5NO_2$.

5. Glycerita (Glycerina, B.P.).—Solutions in glycerin.

Glycerin has good solvent power for many substances. It keeps well, and is useful especially for external application on account of its adhesiveness.

Glyceritum Ac. Carbol., 20 %.
Boroglycerini, 31% of boric acid.

6. Oleata.—Solutions of bases (metallic or alkaloidal) in oleic acid. They are not definite chemic compounds, as the name would imply. The rationale of their use is, that a substance is not absorbed by skin from aqueous, but from oily solutions. Many substances, again, are not soluble in oils, but dissolve in oleic acid. The oleates, therefore, constitute a useful class of preparations when it is desired to secure the absorption of a drug through the skin.

Strengths:
Oleatum Hydrargyri = 20% of mercuric oxid.
" Veratrin, 2%.
" Zinci, ZnO, 5%.

7. Collodia.—Solutions of gun-cotton in ethereal fluids. By the evaporation of the solvent they form a film on the skin, and thus act like plasters. Collodia must not be brought near fire.

Collodium Cantharidatum.
" Flexile (Canada turpentine and castor oil).

The base is collodion: This is made by dissolving pyroxolon, 3 parts, in a mixture of 75 parts of ether and 25 parts of alcohol.

Pyroxylon is prepared by the action of HNO_3 on cellulose (cotton) in presence of H_2SO_4. This may result in a number of substitution products, of which dinitrocellulose is official. Hexacellulose is the explosive.

Cellulose: $= C_6H_{10}O_5 \times 2 = C_{12}H_{20}O_{10}$.
Dinitro.: $= C_{12}H_{18}O_8(NO_3)_2$.

$$(2(C_6H_{10}O_5) + 2HNO_3 = C_{12}H_{18}O_8(NO_3)_2 + 2H_2O)$$

Hexa.: $= C_{12}H_{14}O_4(NO_3)_6$.

SOLUTIONS MADE BY EXTRACTION.

8. Infusions.—Aqueous solutions of the soluble principles of vegetable drugs, obtained by brief maceration in hot or cold water.

Unless otherwise directed, the strength should be 5%, and the *Dose* of the non-poisonous infusions is 15 to 60 c.c. (½ to 2 ozs.).

Inf. Digitalis, 1.5% : *Dose*, 4 to 15 c.c. (= 1 to 4 drachms).
Infusum Sennæ Comp. (Black Draught) = Senna, $MgSO_4$, and Manna.

9. Decoctions.—Infusions in which the ingredients have been boiled with water for at least fifteen minutes. When the strength is not specified, it should be 5%.

Infusions and decoctions are especially useful when it is wished to extract some principle which is more soluble in water, or when the therapeutic effect of alcohol or the mechanical incompatibility of alcohol with salts is to be avoided. There are some inconveniences connected with their use: They take a long time to prepare. Like all watery solutions, they spoil quickly, and must, therefore, be made fresh. The decoction can only be used if there are no delicate constituents to be destroyed by boiling.

The solvent being so very cheap and having no action, it is usual to make decoctions considerably weaker than tinctures. In prescribing them the proportion should always be given in case of strong drugs.

Example: Infusum Digitalis, 0.7 : 50.

10. Alcoholic Extracts in General.—The difference between the various groups of alcoholic preparations is mainly one of strength.

Tinctures.—These are fairly dilute solutions, varying from 0.4% to 50%, but for the most part from 10% to 20%.

Liquores concentrati (B.P.) are more concentrated than the tinctures, but weaker than fluid extracts.

Fluid extracts are made of such strength that 1 c.c. = 1 Gm.

Solid extracts are extracts of various kinds evaporated to a semi-solid or solid consistency.

As to the advantages and disadvantages of these respective preparations:

The *tinctures* are probably the best, since the quantity of solvent is sufficiently large to insure complete exhaustion of the drug and to keep the principle in solution; they also avoid the necessity of heat. On the other hand, their strength is perfectly arbitrary, the only rule being custom.

Fluid extracts (*liquid extracts*, B. P.) are valuable as the most concentrated liquid preparations, where such are desired. They present a definite relation to the drug (1 c.c.

equals 1 Gm.), but this is merely of pharmaceutic importance. On the other hand, the heat which must necessarily be used in their preparation is never beneficial. On account of their concentration, precipitates are apt to form on standing, and while these are often inactive, they may contain the active principles. They are also much more subject to precipitation on mixture with other liquids, and the dose is usually so small that they require some such admixture.

Solid extracts are for convenience of administration in solid form; *e. g.*, in pills, ointments, plasters, etc. They are, of course, very concentrated, and heat must be used in their preparation, but this is a necessary evil with solid preparations. Their greatest drawback lies in the very uncertain strength, since it is impossible to give any definite rule as to how far the evaporation should be carried, and when finished they constantly attract or give off moisture.

Abstracts, now no longer official, were more uniform. With them, some inert powder (sugar of milk) was added to the liquid. The evaporation was then carried to dryness, and then sufficient of the same inert powder was added to bring the weight of the finished product up to a definite relation to the crude drug—*i. e.*, 2 : 1. Manufacturers now make similar preparations, "powdered extracts": *i. e.*, extracts evaporated to total dryness and then mixed with inert powder to come up to what is considered the average solid extract. These are an improvement, for they give uniformity in the preparations of the same manufacturer, but altogether too much is left to his interpretation of the meaning of an "average extract." The foregoing remarks apply only to active extracts. Such extracts as gentian and taraxacum are practically used only as pill excipients, and have very little, if any, therapeutic properties and their strength is immaterial.

Wines are tinctures in which wines have been substituted for alcohol. They have a more pleasant taste, but inferior keeping qualities.

Vinegar (dilute acetic acid) is a good solvent for many substances, particularly alkaloids, and is a fair preservative. It has a tendency to derange digestion and possesses other therapeutic properties which are for the most part objectionable. These preparations (*Aceta*) may be considered antiquated. These remarks hold also for "acetic extracts."

Syrups are practically infusions or decoctions preserved by sugar. They are necessarily dilute, but present a pleasant form of permanent aqueous extracts. The therapeutic effect of the sugar may also be desired—*e.g.*, in cough.

Oleoresins are ethereal extracts made by exhausting the drug with ether and allowing the solvent to evaporate. They contain those portions soluble in ether—mainly oils and resins, hence the name.

Artificial resins are precipitates obtained by mixing alcoholic solutions with water. Where they constitute the active principle, this is a convenient method of isolating it in a concentrated although somewhat impure form. Their strength is fairly constant.

Since drugs are supposed to lose some of their activity by drying and keeping, a class of tinctures made from the freshly collected green drugs has been introduced under the name of *Tincturæ Herbarum Recentium*. These preparations are not at all popular; in fact, almost unknown, and justly so. They are of very inconstant strength, since the natural moisture of plants is variable. Again, they can only be prepared in the localities where the plants are native and where there often are no reliable facilities for their manufacture. These remarks apply equally to *Succi* of the British Pharmacopœia, made by using one part alcohol and three parts of the expressed juice.

The directions of the U.S.P. are to macerate 500 Gm. of the fresh herb with 1000 c.c. of fresh alcohol for fourteen days, to express and filter. The B.P. directs 3 parts of the freshly expressed juice to be diluted with 1 part of alcohol.

11. **Tincturæ.**—Alcoholic or partly alcoholic solutions of the useful constituents of such drugs as are not wholly soluble in the menstruum.

Exceptions to this definition are tincture of iodin, tincture of chlorid of iron, and tincture of tolu.

Tinctures are prepared by solution, maceration, digestion, or percolation, in the manner already indicated. Some dispensers prepare tinctures extemporaneously by diluting fluid extracts. It is scarcely necessary to point out that this procedure is not to be recommended. The whole object of prescribing tinctures, which differ in their composition from the fluid extracts, is thus lost.

Tinctures are usually made by exhausting a given amount of the drug with menstruum sufficient to make a specified quantity. Thus, 15 Gm. of drug, extracted with alcohol q. s. 100 c.c., is spoken of as a 15% tincture. In recent years, however, it has been attempted to introduce more exactitude into this method by assaying the finished tinctures for their active constituents. As these methods are usually rather complicated, the process has thus far been confined to opium, cinchona, and nux vomica (U.S.P.), and a few others (B.P.), but it is expected that the revisers of the Pharmacopœia will add to this number. (See p. 85.)

Ammoniated tinctures—viz., ammoniated tincture of guaiac, and ammoniated tincture of valerian—are those in which aromatic spirits of ammonia is used as a menstruum. In the *ethereal tinctures* the menstruum is ethereal spirit consisting of a mixture of seven parts of ether and three parts of alcohol.

The following is a list of the *strength* in per cent. of the most important tinctures:

	(U.S.P.)	(B.P.)
Tr. opii camph.	0.4% = 2 grs. per oz.	←
" nucis vomic.	2% of extract	¼% strychnin
" cantharidis	5% of the drug	1¼% of the drug
" strophanthi		1½% "
" opii	10% "	4 % "
" " deodor.		. . .
" " et ipecac.		. . .
" belladonnæ fol.	15% "	7 % "
" cannabis ind.		5 % "
" colchici sem.		20 % "
" digitalis		12½% "
" gelsemii		10 % "
" hyoscyami		10 % "
" physostigmatis		. . .
" stramonii sem.		20 % "
" cinchonæ	20% "	20 % "
" lobeliæ		. . .
" aconiti	35% ! "	5 % ! "
" veratri viridis	40% "	. . .

12. **Medicated wines** are tinctures or solutions made with wine as a solvent. Dry white wine of 10% to 14% by weight of alcohol is employed for this purpose, and sufficient alcohol is added to insure permanent keeping qualities—*i. e.*, 15 parts per 100. In the case of vegetable drugs they are prepared by percolation; in the case of chemicals, by simple solution.

13. **Fluid extracts** (liquid extracts, B.P.) may be defined as fluid alcoholic preparations of vegetable drugs, of such strength that 1 c.c. contains the active ingredients of 1 Gm. of the drug.

They are invariably prepared by percolation. (See p. 57.) The drug is moistened, packed in the percolator, and macerated in the usual manner. The first four-fifths of the percolate—that is to say, 800 c.c. for each kilogram of the drug which is being operated upon—are set aside. The percolation is then continued until the drug is exhausted of its active principle (cf. p. 58). This last portion of the percolate is then evaporated to the consistency of a soft extract, and this residue is mixed with the reserved portion, and menstruum is added up to 1000 c.c. In this manner the deleterious effect of heat upon the main mass of the active ingredients which are contained in the reserved portion is avoided.

The heating may also be avoided by the process of *repercolation.* In this, the last portion of the percolate, instead of being evaporated, is used in exhausting new portions of drugs. This is an especially useful method when the finished product is capable of standardization.

Solid extracts must not be confused with the fluid extracts. They are solid or semisolid preparations obtained by evaporation of solutions of the medicinal principles of drugs.

Here it is again attempted to avoid the prolonged action of heat upon the main mass of the constituents by reserving about the first fourth of the percolate, evaporating the remainder, mixing with the first fourth, and again evaporating, this time at a low temperature (50° C.).

It must be remembered that the solvent is of extreme importance in the preparation of solid extracts. If an inappropriate solvent is used,—as, for instance, water in the case of a drug which contains much gummy matter together with an active alkaloid,—the yield of extract will be very large, but it will be very poor in the active substances; whereas if an alcoholic solvent be used, a very small amount of very active extract will be obtained. It will be very readily understood that these preparations, unless extremely carefully prepared, are often unreliable. In the first place, the extent to which the extract must be evaporated cannot be described with absolute accuracy. Then, as already stated, these preparations are very apt to absorb or give off moisture, and thus change their weight.

The prolonged heat to which extracts must necessarily be subjected is very liable to injure the more delicate constituents. It follows from this that solid extracts of poisonous drugs should never be prescribed unless they have been standardized, either by chemic or physiologic tests. The former Pharmacopœia attempted to remove some of the objections to these preparations by introducing the *abstracts,* which were adjusted in such a manner —by dilution, with sugar of milk or some other inactive substance—that 1 Gm. of the extract was equal to 2 Gm. of the drug. For some reason difficult to understand, these preparations never became popular, and have been abandoned. The powdered extracts prepared by some manufacturers avail themselves of the same principle.

Inspissated juices (extractum viride, B.P.) may be placed in this same class. They are obtained by evaporating the expressed juice of the fresh plant.

Extracts may be divided, according to their consistency, into pillular (soft) and hard (dry). The first form a soft mass of the proper consistency to be formed into pills; the latter are dry and brittle, so that they may be pulverized. According to the menstruum employed, extracts may be divided into alcoholic, hydro-alcoholic, and aqueous.

The **artificial resins** are prepared by extracting the drug with alcohol and precipitating with water. The eclectic resinoids are prepared in the same manner, and are, of course, only of value if the active ingredients of the plant are insoluble in water but soluble in alcohol.

14. **Syrups** are dense saccharine solutions of medicinal substances.

Their value lies in the fact that concentrated solutions of sugar form an excellent preservative, since sugar withdraws moisture, and thus prevents the development of organisms. Simple syrup is practically a saturated solution, and contains 85 Gm. of cane-sugar in 100 c.c. Syrups are usually prepared by first making an infusion, and dissolving in this the sugar, either by heat or by percolation, according to whether or not the drug is injured by a high temperature. In special cases modifications may be introduced. *Honey* is sometimes used instead of cane-sugar, making a class of preparations called *mellita*. If acetic acid is added to this, we have *oxymellita*.

Elixirs are aromatic, sweetened spirits, which may be medicated.

They are very useful, since they combine the solvent properties of alcohol and of water, and are very agreeable to the taste. The most useful and best aromatic elixir is flavored with orange peel, lemon, coriander, and anise.

Confections are thick medicated jams.

They were formerly very popular, but have now been almost abandoned. *Electuaries* were similar but somewhat thinner preparations.

15. **Aceta** are medicated vinegars.

At present dilute acetic acid is used as a substitute, since it keeps better and has a more definite strength. Vinegar, or dilute acetic acid, is a good solvent for alkaloids and glucosids, but does not keep as well as alcohol. These preparations are now practically obsolete. They are made of a strength of 10%. *Acetic extracts* are made of the same strength as fluid extracts.

16. **Oleoresins** are ethereal percolates concentrated by evaporation. They contain the fixed and volatile oils and resins of the drug.

17. **Mixtures,** in the wider meaning of the word, are fluids resulting from the mixture of fluids with other fluids or with solids. They comprise: Linimenta, Misturæ, Emulsa.

If they are intended for external application as counter-irritants, they are called **liniments.**

Mixtures, in the narrow meaning of the term, are generally suspensions of a solid in a liquid, sometimes by the use of a gummy substance.

Emulsions are mixtures of a milky appearance, made by suspending fats, oils, or resinous substances in aqueous liquids by the intervention of some gummy, viscid substance.

The object of emulsification is to break up the insoluble oil into the finest particles and to envelop each of these in a coating of the emulsifying agent, which will keep them from reuniting. This allows of dilution, of the admixture of other substances, and it facilitates absorption. Milk is a natural emulsion in which the butter-fat is kept in emulsion by the casein. It may be taken as a type to which artificial emulsions must conform. The globules must be uniform and of about the same size as those in milk.

Emulsions may be divided into the following classes:

1. Natural emulsions, such as are found ready formed in nature. Instances of these are milk, the yolk of egg, and some plant juices.

2. Gum-resin and seed emulsions; that is, emulsions made from such substances as contain their own emulsifier. Examples of such gum-resins are ammoniac, asafetida, and myrrh. The undried drugs should be used in making these emulsions, since they are largely spoiled by drying. The drugs are reduced to a coarse powder and water is added gradually. Seeds which yield such emulsions are poppy, hemp, and almond.

3. In artificial emulsions an emulsifier must be added. Quite a number of substances may be used for this purpose, the principal ones being gum acacia, tragacanth, yolk of egg, Irish moss, soap bark, and extract of malt. The substance most commonly used is gum acacia. This emulsifier is incompatible with large quantities of alcohol, borax, tincture of iron, or glycerin. It may be used by either the Continental method, in which a nucleus is first formed from gum, oil, and water, and to which the remainder of the water may then be added; or by the English method, in which a mucilage is first made, to which the oil and water are added in alternate small portions. The *Continental method* deserves the preference. To form a nucleus there should be used for each part of oil one-fourth to one-half part of acacia and one part of water. Stir the oil with the acacia in granular powder, then add the water at once. The mixture of the oil and the gum must not be allowed to stand too long before adding the water, otherwise it will cake. In the *English method* the acacia, the amount of which should be half that of the oil, is rubbed up with an equal volume of water and then small portions of oil and water are added alternately. If this addition should be done too rapidly, there is danger that the emulsion will separate or "crack." This does not necessarily spoil it, for it may be re-emulsionized by adding it to a fresh portion of acacia and repeating the process.

In making medicated emulsions the ingredients should be mixed in the following order: First the nucleus, then the flavoring, then the syrup, and, lastly, the water in which the solids have been dissolved.

In *yolk emulsions*, the yolk of egg is used in place of the nucleus in the Continental method. The yolk is triturated in a mortar and the oil and water are added alternately in small portions. One yolk suffices for from one to two ounces of oil. The yolk emulsions are incompatible with the same substances as gum emulsions and do not keep nearly as well.

Soap bark has saponin for its emulsifying agent. It is not incompatible with any of the above-named substances, but possesses very decided therapeutic properties, which preclude its use in many cases. It is used in the proportion of 1 part of the tincture to 8 parts of the oil: Place the tincture in a dry bottle, add the oil in portions, and shake after each addition. Finally add the water. Crude saponin (0.3 : 100 of oil) can also be employed.

Extract of malt emulsifies its own weight of oil. It is used as the nucleus in the Continental method.

Solutions of alkalies may also be used for emulsification, since they form soaps, but they are usually not desirable.

SOLID PREPARATIONS.

18. Powders are finely powdered drugs intended for either external or internal administration.

When intended for external use, as for dusting-powders, extreme fineness is the main desideratum. They should in this case be mixed with a spatula and not in a mortar, since the former insures greater smoothness. When intended for internal use, they are generally folded in papers. It must be borne in mind that no hygroscopic substances, such as potassium acetate or citrate, can be prescribed as powders. Camphor and chloral become fluid when mixed together. In making compound powders, one should begin with the smallest ingredient and add the others in the order of their amount, triturating thoroughly after each addition. In dividing the powder, it is not usually necessary to weigh out each powder. The object is generally accomplished with sufficient accuracy by flattening the powder on a piece of paper, squaring off the edges, and dividing into a number of equal parts by means of a spatula. In the case of more bulky powders, such as Seidlitz powders, measures are used. Most of the official powders are now obsolete. The important ones are:

Pulvis Cretæ Comp. = prepared chalk, acacia, and sugar.
“ Effervescens Comp. (Seidlitz powder) = $\left\{\begin{array}{l}\left.\begin{array}{l}\text{NaHCO}_3,\ \ 2\tfrac{1}{2}\text{ Gm.}\\ \text{Rochelle salt, }7\tfrac{3}{4}\text{ Gm.}\end{array}\right\}\text{ blue paper.}\\ \text{Tartaric acid, }2\tfrac{1}{4}\text{ Gm.} = \text{white paper.}\end{array}\right.$
“ Glycyrrh. Comp. = senna, licorice, fennel, and sulphur.
“ Ipecac et Opii = 10% of each.

Granular Effervescing Salts.—These are a pleasant form of administering many salts, the CO_2 helping to disguise the taste, and favoring absorption and peristalsis. The basis is a mixture of sodium bicarbonate and tartaric acid or citric acid; to these is added the medicinal agent and sugar enough to make the dose a teaspoonful. This mixture is softened by heat or moistened with alcohol, well stirred until solid, and pressed through a sieve.

Triturations are powders obtained by triturating the active substances with some inert material such as sugar of milk.

Their advantage lies in the greater ease in weighing out a comparatively large amount of substance. When no special directions are given, triturations are made of a strength of 10%. The trituration of elaterin is the only one officinal.

Eleosacchara are triturations of volatile oils with sugar in the proportion of 1 : 30. They are used for the purpose of flavoring other powders.

To get a definite dose and to reduce the bulk of the substances where it is desired to administer them in dry form, and when the inconvenience of powders is to be avoided, we employ lozenges, triturates, pills with various coatings, capsules, wafers, or cachets. The administration of substances in dry form always delays their absorption, and this is especially the case if the preparations are coated. On the other hand, they have the advantage of reaching the intestinal canal with little change. One must always be careful not to prescribe pills, etc., of such bulk that they cannot be swallowed.

19. **Pills** may be defined as spherical or elongated masses of medicinal substances, of such size as to be convenient for swallowing; that is to say, containing up to 5 grs. (0.35 Gm.) of active substance. If the pill is of larger size, it is called a *bolus*. Very small coated pills are spoken of as *granules*.

A pill consists of the active ingredient and of the *excipient* (cohesive); the latter varies with the nature of the former.

In order to make pills, the substance is first made into a *mass* by means of this excipient. The mass must be sufficiently soft to admit of molding, but on the other hand it should be sufficiently consistent not to lose its shape. It should neither harden nor soften nor crumble on keeping.

Method of Preparation.—The ingredients are first triturated to a fine powder. In case crystalline salts are used, these must first be desiccated. The excipient is then added in small portions and thoroughly triturated with the powder until the proper consistency is obtained. If accidentally too much excipient is added this can be remedied by the addition of some inert powder, such as starch, gum acacia, or powdered licorice. A great many substances may be used for excipients. The following are the most useful:

Liquid Excipients.—Glycerid of acacia or tragacanth, thick flour paste, glycerin, syrup, confections, or extracts.

Solid Excipients.—Acacia, tragacanth, starch, althæa, licorice powder, soap.

For chemicals which are destroyed by organic substances the best excipient is formed by a mixture of petrolatum and kaolin.

The weight of the finished pill should not exceed 0.5 Gm. (8 grains).

The mass having been formed by thorough trituration, it is placed on a glass or porcelain slab marked with equal divisions. It is well to put a little dusting-powder on the slab to prevent the mass from sticking to it. The best dusting-powders are starch, lycopodium, or licorice, according to the color of the pill mass. This mass is then rolled out by means of a broad spatula into a cylinder of uniform diameter, and this is cut with a sharp knife into the requisite number of equal parts. These are formed into spherical shape by rolling them between the thumb and the first two fingers. The finish may be rendered more perfect by placing the pills with a liberal amount of dusting-powder in the lid of the pill box and gently rolling them with the ball of the thumb. To disguise the taste of the pills one may make use of various coatings. The most popular of these are the sugar and the gelatin coatings. These can only be well done on a large scale. For the former, the pills are moistened with a thick syrup and rapidly rotated and dried in a current of warm air until they acquire a sufficiently thick coating and a fine polish. The latter is often enhanced by a little wax. For a gelatin coating they are dipped into a strong hot solution of gelatin, which is allowed to harden in the air. When it is desired to exclude the air from the pills, they are sometimes varnished by dipping them into an ethereal solution of tolu. This is the official process for keeping phosphorus pills. A still finer polish may be given to pills by coating them with silver leaf, which is done by shaking them in a box with silver foil. All of these coatings interfere with the absorption of the active substances, but this is indeed a disadvantage which adheres even to the uncoated pill. In some cases it is highly desirable that the pill reach the intestinal canal without any change—namely, when we desire a local action upon the intestinal canal alone. The following coatings may be employed for this purpose: (1) Keratin, which is made by dissolving goose-quill in acetic acid or sodium hydrate. (2) Salol. Both of these are partly dissolved in the stomach. (3) Glutoid capsules have also been recommended. They are gelatin capsules which have been hardened in formaldehyd.

The **pilulæ** of the B.P. are pill-masses (*massa*, U.S.P.).

The composition of the most useful pills will be given under their respective constituents.

Troches (*trochisci*) are made by punching or cutting out circular or oblong disks from a mass made up from the active substance, sugar, and mucilage. These are then dried in the air. They are usually intended for solution in the mouth, and are most popular for throat medication. They are, however, sometimes used instead of pills.

Trochisci Santonini (½ gr. = 0.032 Gm. U.S.P., 1 grain B.P.).

Tablet triturates are small troches made from a mass of sugar and dilute alcohol. This mass is spread into holes in a special form and then removed from these by means of a die. They have the advantage over pills of a very much greater solubility.

Compressed tablets are made by compressing the substance diluted with sugar or sugar of milk. The material must be in granulated form. They do not break as readily as the triturates, but, on the other hand, they are not as soluble.

Lamellæ (B.P.) are thin gelatin disks, softened with glycerin, and impregnated with substances acting on the pupil. They are intended to be placed under the eyelids.

20. Suppositories are suitably shaped masses of solid, medicated, fatty substances, intended for introduction into the rectum, vagina, or urethra. They take the place of ointments for local treatment where these cannot be readily applied.

Suppositories are made by incorporating the medicinal substance into a suitable base, and molding into masses of suitable shape and size. The ideal base is one which, whilst solid at the ordinary temperature, is melted by the heat of the body. Such is cacao-butter (Oleum Theobromatis). Gelatin or a soapy base is also sometimes used, especially with urethral suppositories, for which cacao-butter would be too brittle. They are made either by the hot or cold process. The hot process consists in melting cacao-butter at a temperature not exceeding 35° F. and adding the active substances, then pouring the mixture into cold molds. If the molds are sufficiently cold, the finished suppositories can be removed without any difficulty. It is usually advisable, however, to employ a small amount of dusting-powder. In the cold process the active substances are triturated with grated cacao-butter with the addition of a small amount of castor-oil, sufficient to make it into a suitable mass, which is then rolled out and divided as for pills. They may also be formed by pressure. *Suppository capsules*, whether of gelatin or of cacao-butter, largely defeat the object for which suppositories are employed. They are, however, much more convenient to prepare than the suppositories, and may suffice when the object is merely internal medication.

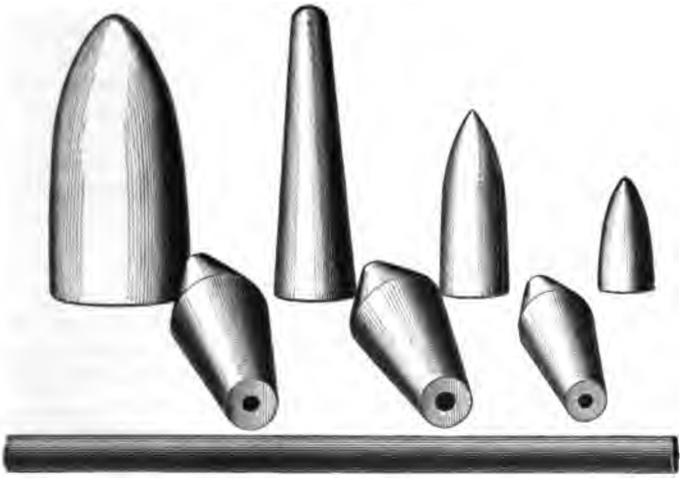

Fig. 43.—Different forms of suppositories (H. Blair). Natural size: The largest is for use in the vagina; the cylinder is a urethral suppository or bougie; the others are various shapes and sizes of rectal suppositories.

Glycerin is made into a suppository by means of a very hard soap formed from stearic acid and sodium carbonate.

The weight of suppositories should be: For rectal or urethral use, about 1 to 2 Gm.; for vaginal use, about 3 Gm.

21. Ointments (*Unguenta*) are soft fatty masses intended for external application. They consist of the active ingredient and the base.

The base of ointments is formed by lard, by petrolatum, by lanolin, or by various mixtures, of which the simple ointment, consisting of 4 parts of lard and 1 part of yellow wax, is the most important. The base must vary according to the object for which the ointment is employed, whether absorption, protection, or local action is desired. *Petrolatum* (vaselin), which consists of the less volatile parts of petrolatum, is simply protective, or useful as a vehicle for substances intended to have a mere local action, since it is not absorbed. *Lanolin*, or its pharmacopœial substitute, Adeps Lanæ Hydrosus, consists of a mixture of cholesterin-like substances obtained from sheep's wool. It is very readily absorbed, does not become rancid, and mixes with its own weight of water. This latter property is of great advantage when it is desired to use crystalline salts in ointment form, since these can be incorporated in the form of solution, making a much smoother ointment. *Lard* is the cheapest ointment material. It possesses, but in a lesser degree, the advantages of lanolin. An important objection to it rests upon the fact that it becomes rancid very rapidly. This tendency can be greatly diminished by the incorporation of antiseptic substances. Official Benzoinated Lard is an attempt in this direction.

Ointments are prepared by fusion, mechanical admixture, and chemic reaction. In mixing ointments by fusion, that constituent of the ointment which has the highest melting-point is first melted, and the others are then added in the order of their melting-points. The active substance is added last, to obviate the prolonged action of heat upon it. The mechanical admixture is usually done on a slab or in a mortar. It is needless to say that powders must be in the finest stage of subdivision. If the quantity of powder is large, it is usually first mixed with some of the melted ointment.

The strength of the more important official ointments is as follows:

	U.S.P.	B.P.
Unguentum Simplex: Lard, 4; yellow wax, 1.		. . .
" Acidi Carbolici	5%	4%
" " Tannici	20%	. . .
" Chrysarobini	5%	4%
" Hydrargyri	50%	50%
" Iodi	5%	5%
" Iodoformi	10%	10%

Cerates (U.S.P.) are preparations similar to ointments but of a firmer consistency. They are made from a mixture of wax and lard, in the same manner as ointments.

Cerate of cantharides contains 10%.

22. **Plasters** are made by spreading on a thin cloth or leather support a mass or base which is hard at an ordinary temperature, but is softened and rendered adhesive at the temperature of the body. The base is fused and the active ingredients incorporated into it by stirring. Too great a degree of heat must, of course, be avoided. The mass is then usually spread upon pieces of linen, muslin, or leather. Plasters serve to afford protection to the skin, to bring together the edges of wounds, or to bring a drug in an absorbable medium into prolonged contact with the skin. Furthermore, the resins, etc., which frequently form the constituents of the plaster act as mild counterirritants. To avoid the rather excessive irritation resulting from the confinement of the secretions of the skin, plasters are now frequently made porous. The base is now usually made of rubber. The typical old plaster, however, has for its base diachylon, Burgundy pitch, or other resins. Diachylon is a lead soap made by the boiling together of litharge and olive oil. The oil is decomposed, according to the following formula:

$$2C_3H_5(C_{18}H_{33}O_2)_3 + 3PbO + 3H_{20} = Pb_3(C_{18}H_{33}O_2)_2 + 2C_3H_5(OH)_3.$$

Plasters are now usually obtained from manufacturers, and are but rarely made to order. Some masses are official.

To spread the plaster the cloth, cut to the proper size and shape, is tacked on a board and the mass is heated and spread evenly with a trowel or spatula. A margin half an inch wide must be left to allow of handling. Isinglass plaster is made by spreading a thick solution of isinglass on silk.

23. **Cataplasmata** (*Poultices*).—These are used mainly for the purpose of supplying heat. It is often necessary to give a patient directions for preparing them. Linseed poultices may be taken as a type: Pour 4 ozs. of linseed meal into 10 ozs. of boiling water, stirring constantly. Spread the mush thickly on a piece of flannel, fold so as to form a sack, and apply as hot as can be conveniently borne.

TABLE V.—STRENGTH OF PHARMACEUTIC PREPARATIONS.

U.S.P. *Opium:* Tincture, deodorized tincture, acetum, and Dover's powder = 10%; camphorated tincture = 2 grains to the ounce (= 0.4%).

Dilute Alcohol, 41%.

Decoctions and Infusions, 5%.

U.S.P. *Dilute Acids*, 10% (except hydrocyanic = 2%; and acetic = 6%).
U.S.P. *Tinctures*, 2% to 50%; mostly 20%.
U.S.P. *Aceta*, 10%.
Fluid Extracts, 100%.
Arsenic Solutions, 1%.

TABLE VI.—DOSES OF PHARMACOPŒIAL PREPARATIONS.

Decoctions and infusions, ℥j to ℥ij (except infusum digitalis, ʒij to ʒiv).
Aquæ, ℥ss (except ammoniæ and laurocerasi).
Confections, ʒij.
Solid extracts: Non-poisonous, grs. iij to x; poisonous, gr. 1/10 to ½ (except physostigma, gr. 1/16 to ¼).
Fluid extracts: Non-poisonous, ʒss to ʒj; poisonous, ♏j to xv!
Liquors, ♏v to x (except alkaline acetates and citrates, ℥j).
Aromatic oils, ♏v.
Spirits, ʒss to j (except glonoin, ♏j to v).
Tinctures: Non-poisonous, ʒss to ʒiss; poisonous, ♏x to xx (except aconite, ♏ss to v; cantharides, iodin, and strophanthus, ♏ij to x).
Syrups, ʒj.
Wines, ʒss to ʒj (except opium).
Dilute acids, ♏v to xx (except dilute hydrocyanic, ♏ij to iij.
Liquid opium preparations, ♏iij to xx (except camphorated tincture, ℥ss).
Liquid arsenic preparations, ♏iij to x.
Mercuric salts, gr. 1/80 to 1/10.
B.P. Hypodermic injection (B.P.), ♏ij to x.
B.P. Pilula (B.P.), gr. iv to viij.

CHAPTER IV.—(*Continued.*)

(B) PHARMACEUTIC ASSAYING.

THE more active drugs do not act as a whole. Their activity is due only to certain ones of their constituents, to the so-called "active principles." Our knowledge of these is of comparatively recent date. In 1805, Sertuerner isolated the active principle of opium, morphin, and thereby opened up a brilliant field for investigation. Similar substances were isolated from other drugs: Strychnin from nux vomica, atropin from belladonna, quinin from cinchona, etc., and soon a list of very active chemic substances, the *alkaloids*, was compiled, showing a general similarity in their chemic properties.

Another series of very active chemic substances was soon added to these, resembling them in their violent action, but totally dissimilar in their chemic properties: glucosids.

These alkaloids and glucosids are present in plants in more or less stable chemic combination, and are more or less soluble in water or alcohol. To obtain them in solution as free as possible from inactive matter is one of the principal aims of Galenic pharmacy. But even when these solutions are made according to uniform formulas, the products show great differences in the amount of active ingredients—differences depending partly upon variations in the skill and care of the operator, partly on the variations in the crude drug. Thus, one belladonna extract may be four times as strong as another, and yet both may be made after the letter of the Pharmacopœia. As this variability is highly undesirable in the case of powerfully acting drugs, various remedies for it have been devised. The most radical is to isolate and employ the active constituents in the pure condition: *e. g.*, morphin in the place of opium. But in certain cases preparations of the crude drugs are for various reasons more desirable than the isolated principles. In these cases it must be aimed to estimate the active portion by either chemic or physiologic means. Unfortunately neither is an easy matter. Standardization is at the best a time-robbing process, requiring considerable apparatus and skill, and in many cases the results are not trustworthy. With many substances, especially the glucosids, no chemic method has been devised. In other cases we must rest content with the "total alkaloids," which may be a mixture, the parts of which may even show an antagonistic action. For this reason physiologic tests, among the easiest and most accurate being the toxic dose per gram of animal, should also be introduced.

The U. S. Pharmacopœia directs chemic assays at present only with three drugs: opium, cinchona, and nux vomica. It is to be expected, however, that the next edition will contain many more instances. The process depends upon the same principle as that used in the separation of alkaloids—*i. e.*, difference in the solubility of alkaloids and their salts.

To illustrate the general method: If it were desired to determine the alkaloids of cinchona, one would extract the drug with acidulated water. The solution would contain the alkaloidal salts, tannin, coloring-matter, and other extractives. This solution would be shaken with ether. This would extract resins, etc., whereas the alkaloids would stay in the watery solution. The latter would be made alkaline by ammonia and again extracted with ether; the alkaloids, having been liberated from their salts, will pass into the ether, and this will yield, on evaporation, almost pure alkaloids, which can either be weighed directly or titrated alkalimetrically.

The process must be modified in each particular case. The principles are well illustrated in the method of determination of morphin in opium.

Assay of Opium.—The powdered opium is first macerated with water. The purpose of this maceration is to bring the active principles into solution; but besides the morphin, there pass into the solution the other alkaloids, the coloring-matter, and other extractives, such as gum. The purpose of the subsequent manipulations is to separate the morphin in pure form. The addition of ammonia will precipitate all the alkaloids, leaving the greater part of the coloring-matter and extractives in solution. The problem now is to separate the morphin from the alkaloids that have been precipitated with it. To do this, advantage is taken of the fact that morphin is comparatively insoluble in alcohol or in ether. The solubility in alcohol is 1 part in 300; in ether, 1 part in 4000. The other opium alkaloids are quite soluble in these solvents; for instance, narcotin requires but 80 parts of alcohol or 35 parts of ether for solution.

This fact is also taken advantage of in the preparation of the deodorized tincture of opium, where the narcotin, etc., are removed by treating the tincture with ether.

The separation is therefore accomplished by treating the precipitate with alcohol and then with ether, both of which also remove some coloring-matter that has been carried down with the precipitate. Since ordinary alcohol would absorb some of the morphin, the alcohol which is used for this washing has been previously saturated with the powdered alkaloid.

The *details of the process* are the following (U. S. P.):

Introduce 10 Gm. of opium in powder or in small pieces into a bottle having a capacity of about 300 c.c. Add 100 c.c. of water, cork it well, and agitate it frequently during twelve hours. Then pour the whole as evenly as possible upon a filter having a diameter of 12 cm., and when the liquid has drained off, wash the residue with water, carefully dropped upon the edges of the filter and the contents, until 150 c.c. of filtrate are obtained. Then carefully transfer the moist opium back to the bottle by means of a spatula, add 50 c.c. of water, agitate thoroughly and repeatedly during fifteen minutes, and return the whole to the filter. When the liquid has drained off, wash the residue as before until the second filtrate measures 150 c.c., and finally collect about 20 c.c. of a third filtrate.

The purpose of these repeated washings is to remove the extract which is retained in the interstices of the marc.

Evaporate in a capsule first the second filtrate to a small volume, then add the first filtrate, rinsing the vessel with the third filtrate, and continue the evaporation until the residue weighs 14 Gm.

The weak extracts are evaporated first, so as not to expose the main mass of the alkaloid to a prolonged heat, which would injure it.

If the assay were on the tincture, this would first be evaporated to a small bulk. This would have the double purpose of concentrating it and of removing the alcohol. The resins which had been dissolved in the latter would therefore be precipitated, and could be removed by filtration. The remainder of the process is the same as that for crude opium.

The extracts having been evaporated to 14 Gm., the concentrated solution is rotated about in the capsule until the rings of the extract are redissolved. The liquid is then poured into a tared Erlenmeyer flask having a capacity of about 100 c.c. The capsule is rinsed with a few drops of water at a time until the entire solution weighs 20 Gm.; then add 10 Gm. of alcohol, shake well and add 25 c.c of ether, and shake again. Now add 3.5 c.c. of ammonia water (10%) from a graduated pipette or burette; stopper the flask with a sound cork, shake it thoroughly during ten minutes, and then set it aside in a moderately cool place for at least six hours or overnight.

Ammonia is used because the morphin is less soluble in excess of this than in KOH, or NaOH; nevertheless a large excess must be avoided, and the directed quantity is important. The alcohol and ether are added to dissolve out all the alkaloids and extractives except the morphin.

Remove the stopper carefully, and should any crystals adhere to it, brush them into the flask. Place in a small funnel two rapidly acting filters of a diameter of 7 cm., folded one within the other, the triple fold of the inner filter being laid against the single side of the outer filter. Wet them well with ether.

If any water should get on the filter accidentally, the ether would not run through it.

Decant the ethereal solution as completely as possible upon the inner filter, add 10 c.c. of ether to the contents of the flask, rotate it, and again decant the ethereal solution upon the inner filter. Repeat this operation with another portion of 10 c.c. of ether; then pour into the filter the liquid in the flask in portions in such a way as to transfer the greater portion of the crystals to the filter. When this has passed through, transfer the remaining crystals to the filter by washing the flask with several portions of water, using not more than about 10 c.c. in all. Allow the double filter to drain, then apply water to the crystals drop by drop until they are practically free from mother-water, and afterward wash them drop by drop, from a pipette with alcohol previously saturated with powdered morphin. When this has passed through, displace the remaining alcohol with ether, using about 10 c.c., or more if necessary.

This should be done quickly, as the ether is to prevent the alcohol from evaporating and leaving its morphin.

Allow the filter to dry in a moderately warm place, at a temperature not exceeding 60° C., until its weight remains stationary. Then carefully transfer the crystals to a tared watch-glass and weigh them. The weight found, multiplied by 10, represents the percentage of crystallized morphin obtained from the opium.

In estimating other alkaloids, as in cinchona or extract of nux vomica, use is made of immiscible solvents. The alkaloid is dissolved out by acidulated water, precipitated by the addition of an alkali, and this mixture is then shaken with chloroform, which is allowed to separate and removed by a separating funnel. The alkaloid in this chloroformic solution is then estimated, either by evaporating the solution (cinchona) or else by determining its alkalinity (nux vomica).

Keller's Method.—Another method which has not so far been adopted in the Pharmacopœia, but which gives promise of good results, is that devised by Keller. The principle of the method is the following: The drug in powder is put with ether or a mixture of ether and chloroform—liquids which penetrate the drug with great readiness. An alkali is added so as to liberate the alkaloids and cause them to dissolve in the ether. Some water is then added and a part of the ethereal solution is decanted. The alkaloids of this solution are taken up by acidulated water, again liberated by alkali, dissolved in ether or chloroform, and, finally, obtained in substance by the evaporation of the solvent.

The advantages of this process are, firstly, that it does not require any complicated apparatus; a few separating funnels, flasks, medicine vials and graduated cylinders, and a small distilling apparatus suffice; secondly, it is possible to complete the examination of the drug in a few hours; and, thirdly, it gives the alkaloids in a greater degree of purity than any of the other methods. This is due to the fact that alcohol is entirely avoided and that alkalies and acids act only at the ordinary temperature, and for so short a time that no alteration of the alkaloids need be feared.

The following are the *details* of the method: A quantity of the drug weighing, according to its richness in alkaloids, from 10 Gm. to 25 Gm. is taken. This should be in a fairly fine powder and thoroughly dried at a low temperature; best of all, in a desiccator. The extraction is done in a medicine glass of a content of 200 to 300 c.c. The extractant is pure ether, or a mixture of 75 to 80 parts of ether with 25 to 20 parts of chloroform. It usually suffices to macerate the drug for five to ten minutes with the solvent, with occasional shaking, before adding the alkali. In a few cases it is necessary to first remove the fat by extraction with ether in an ordinary funnel, or in a Soxhlet apparatus. Aqua ammonia of 10% is taken as the alkali. After the addition of the alkali the vial must be thoroughly shaken for a short time so that the drug is moistened. The maceration is then continued with occasional shaking during half an hour. A certain quantity of water is now added; this quantity varies for the different drugs. If the mixture is now shaken violently during two or three minutes, the powder will be found to become agglutinated, and the greater part of the ether solution can be decanted perfectly clear. If any difficulty should arise in decanting the prescribed quantity, as much as possible of the ether is poured off, the flask is again corked and shaken while in a horizontal position, and allowed to lie quietly for a short time. In this way it is always possible to obtain the required quantity. This ethereal solution contains, besides the alkaloids, some fat, wax, resin, coloring-matter, and other extractives. To remove these, it is shaken in a separating funnel with three successive portions of 25, 15, and 10 c.c. of dilute hydrochloric acid of the strength of 0.5% to 1%. The acid watery solutions are again poured into a separating funnel, made alkaline with ammonia, and extracted at once with a mixture of 3 parts by weight of chloroform and 2 parts of ether or with pure ether. It is best to add the solvent first and then the ammonia; about 100 Gm. of the solvent will be required. This extraction can be done quite rapidly. The pure ether is somewhat more difficult to handle, but gives better results than the mixture. The united solutions are allowed to stand for a short time and then filtered through a small filter moistened with ether and the solvent is distilled off. The alkaloids can then be weighed directly, or, best of all, be titrated alkalimetrically after solution in alcohol, using hematoxylin as indicator.

CHAPTER IV.—(*Continued.*)

(C) TABLES OF INCOMPATIBILITIES AND SOLUBILITIES.

I. INCOMPATIBILITY.

THIS is a subject usually very confusing to the student, since it consists of what appears at first sight a vast array of details. However, it rests only upon an application of the ordinary chemic reactions, and when the latter have been mastered, the subject is comparatively easy and simple. It may be laid down as a general rule that substances are incompatible if they are used in testing for each other or if they form antidotes.

In the following compilation it has been attempted to arrange the incompatibilities into general groups.

Incompatibility is said to exist *when the constituents of a mixture interfere with one another in a way not intended by the prescriber.*

If such an interference is intentional, it is called an *intentional incompatibility*, as in the preparation of yellow wash.

When it consists in a precipitation of the substance by a change in the solvent, or when a chemic incompatibility does not interfere with the active substance, but produces an unsightly appearance, it is *pharmaceutic.*

When without causing any chemic changes it interferes with the physiologic action of the ingredients, it is *therapeutic.*

TABLE VII.—THE MOST IMPORTANT INCOMPATIBILITIES, ARRANGED BY GROUPS.

Incompatibility.—(A) Chemic; (B) Pharmaceutic; (C) Therapeutic.

(A) Chemic Incompatibility.—(I) Explosive; (II) Precipitation; (III) Production of body with undesired properties.

I. Explosives.—

1. Spontaneously inflammable substances (phosphorus).
2. Substances which explode on heating ($KClO_3$).
3. Substances which explode on mixing (**3**). (See below.)

4. Substances which cause a more gradual evolution of gas (4).

5. Substances which cause an evolution of heat (H_2SO_4 and water).

6. Substances which should be guarded from fire (ether, alcohol, benzin, collodion, turpentine, camphor, essential oils, etc.).

3. SUBSTANCES WHICH EXPLODE ON MIXING: [1]

(*a*) *Substances containing loosely combined oxygen,* such as: *Chromic acid; Concentrated nitric acid and nitrates; Permanganates; Chlorates, bromates, or iodates* (in order of violence)—
with easily oxidizable substances, such as: All organic substances; Sulphur, sulphids, sulphites, and hyposulphites; Iodin and iodids; Phosphorus, phosphites, and hypophosphites; Reduced iron.

(*b*) *Iodin* (with any oxidizing agent); also with Ammonia or turpentine.

(*c*) *Chlorin:* with NH_4Cl.

4. SUBSTANCES WHICH CAUSE A GRADUAL EVOLUTION OF GAS:
HCl with HNO_3.
Strong acids with $KClO_3$ (Cl).
Strong acids with alcohol (ethers).
Acids with carbonates (CO_2).
Acids with sulphids (H_2S).

II. Incompatibility by Precipitation.—

1. The following INORGANIC BASES or their salts precipitate the following INORGANIC ACIDS or their salts:

(*a*) *Salts of metals and earths* are precipitated by HO, O, CO_2, P_2O_5, BO_3, oxalic acid, and the corresponding salts of alkalies.

(*b*) *Salts of metals:* by the above salts of earth.

(*c*) *Salts of metals:* by mercury salts.

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[1] EXPLOSIVE MIXTURES:

Explosions will only occur when the substances are dry, or at least concentrated, and when they are heated or percussed.

Dilute solutions may be mixed without danger if not heated. Glycerin, phenol, and in some cases alcohol, behave like dry solids.

Permanganate of potash or chromic acid or nitrate of silver will decompose organic substances even in solution, but in this case without explosion.

Powders may be mixed without concussion, but even this should be avoided, since conditions favorable to explosion may arise after they leave the hands of the dispenser.

Pills containing these easily decomposed substances are best made with inorganic excipient (clay and vaselin).

Substances containing loosely combined oxygen may explode on concussion or heat when no reducing substances have been added; this is due to their containing dust or other organic matter. They should therefore be handled with care.

(*d*) *Salts of Ag, Hg* (*ous*), *Pb, Bi, Sb:* by Cl, Br, I.
(*e*) *Salts of Ag, Hg* (*ous*), *Pb, Bi, Sb, Ca, Sr, Ba:* by SO_4.

2. The following SALTS OF METALS precipitate the following ORGANIC SUBSTANCES:

(*a*) *All metallic salts:* proteids, gelatin, tannin, acacia.
(*b*) *Some metallic salts* (especially double salts): alkaloids.
(*c*) *Silver salts:* all organic substances.
(*d*) *Iron salts:* salicylic or carbolic acid or their salts produce a purple color.

3. ORGANIC SUBSTANCES: The following incompatibilities by precipitation are important:

(*a*) *All* are incompatible with oxidizing agents (compare explosives) and with silver salts.
(*b*) *Alkaloids, proteids, gelatin, and tannin* are precipitated by each other, and by
    Many metallic salts, especially mercuric.
    Double iodids and free iodin.
    Picric and salicylic acid.
  Alkaloidal salts, in addition, by free bases and carbonates.
  Strychnin salts, by bromids and iodids.
  Acacia, by alcohol, borax, Tr. ferri chl.
(*c*) *Antipyrin:* by same precipitants as alkaloids.
    By KI.
    Fe_2Cl_6 = reddish color.
    Spirits of nitrous ether = green color or precipitate.
(*d*) *Chloral:* when in alcoholic solution by strong solutions of salts, especially bromids.
    Alkalies cause decomposition.
    Camphor, in dry state = liquefaction.
(*e*) *Salicylic acid* by iron salts.
    Iodids.
    Alkaloids.
  Salicylates by free acids.
(*f*) *Tannin* by metallic salts.[1]
    Alkaloids.
    Gelatin and albumin.
    Carbonates.

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[1] The incompatibility of *tannin with iron* is especially important, since it is often desirable to administer iron salts with a bitter substance. Practically the only tannin-free bitters are *Calumba*, *Quassia*, and *alkaloids*.

De-tannated preparations, such as the *Elixir of Gentian* N.F., may also be employed.

III. Production of a Substance with Undesired Properties.—

(*a*) Iodids, Bromids, Iodates, Bromates, Chlorates: with strong mineral acids or strong oxidizing agents, such as $KClO_3$, H_2O_2, HNO_3, KMnO = production of I, Br, or Cl.
(*b*) Glucosids with acids.
(*c*) Chloral with alkalies.

(B) Pharmaceutic Incompatibilities.—

1. *Alcohol* should not be added to:
   Acacia, gelatin, proteids, emulsions, strong salt solutions.
2. *Water* should not be added to:
   Alcoholic liquids in general (such as tinctures, spirits, fluid extracts).
   Ethereal liquids (oleoresins), oils.
   (Carbolic acid should not be mixed with collodion.)
3. *Glycyrrhiza* and acids.

The following drugs are ***almost universally incompatible***, and should therefore be prescribed alone, if possible:

Strong mineral acids,
$HgCl_2$,
KI,
$AgNO_3$,
$Pb(C_2H_3O_2)_2$,
$KMnO_4$,
Alkaloids,
Tannin.

(C) Therapeutic Incompatibility.—

For example: Pilocarpin and atropin.

II. SOLUBILITIES.

It is well to have a general idea of the solubility of the substances usually prescribed. The subjoined compilations will be found useful in this connection. A knowledge of analytic chemistry and of incompatibilities can also be utilized here, for a substance appearing as a precipitate is, of course, relatively insoluble.

TABLE VIII.—GENERAL SOLUBILITY OF SALTS IN WATER.

Only those commonly prescribed are included (not those which are formed only in incompatible prescriptions).

I. Arranged by Acids.—

Group A: Salts Mostly Soluble.—

1. *Acetates and Nitrates:* all soluble.
2. *Halogen group* (= iodids, bromids, and chlorids): Soluble, except Ag; Hg (ous); Pb; Bi.
3. *Sulphates:* Soluble, except Pb and Ba; Ca sparingly soluble.
4. *Tartrates and Citrates:* mostly soluble.

Group B: Salts Mostly Insoluble.—

1. *Arseniates*
Arsenites
Carbonates
Hydrates (Ca sparingly soluble)
Oxids
Oxalates
Borates
Phosphates
} Insoluble, except those of alkali metals.

II. Arranged by Base.—

The salts considered in this table are: Acetates (Ac), Halogens (H), Oxids (O), Sulphates (SO_4), Phosphates (P_2O_5), Oxalates (Ox), Carbonates (CO_2), Sulphids (S), Nitrates (NO_3), Citrates (Ci). Hydrates agree with oxids.

Those of the above salts which are *not mentioned* with the respective base are *insoluble*.

1. *Alkali Metals* (= Na, K, NH_4): all soluble.
2. *Lithium:* Soluble, except O and CO_3, sparingly soluble, and P_2O_5, insoluble.
3. *Mg, Al:* Soluble: NO_3, Ac, H, Ci, SO_4, S, O.
4. *Ca, Ba, Sr:* Soluble: NO_3, Ac, H, Ci, S; O, SO_4, sparingly.
5. *Zn, Mn, Ni, Co, Fe*
Hg (ic), Cu, Sn } Soluble: NO_3, Ac, H, Ci, SO_4 (mercuric iodid is insoluble).
6. *Bi, Sb:* NO_3, Ac, H, sparingly soluble.
7. *Hg (ous), Ag, Pb:* Soluble: NO_3, Ac.

III. Solubilities of Important Substances in Usual Solvents.—

At 15° C. (60° F.) one part of the substance dissolves in:

	WATER.	ALCOHOL.	GLYCERIN.		WATER.	ALCOHOL.	GLYCERIN.
Acid, boric . . .	25	15	10	Pot. chlorate . .	16.7	sp.	
" carbolic .	20	freely	freely	" iodid . . .	0.75	18	
" tannic . .	1	0.6	2	Quin. sulphate .	740	65	
Alum . . .	9	insol	2.5	" bisulphate	10	32	
Amm. chlorid .	3	sp. sol		$AgNO_3$	0.6	26	
Tartar emetic . .	17	insol		Sod. acetate . .	1.4	30	
Antipyrin . . .	1	1		" bicarbonate	11.3	insol	13
Chloral	v. s.	v. s.	v. s.	" borate . .	16	insol	2
Iodin	5000	10	50	" bromid . .	1.2	13	
$HgCl_2$	16	3	4	" iodid .	0.6	3	
Hg_2Cl_2	insol	insol		" salicylate .	0.9	6	
Morph. sulph. .	21	702		Strychn. sulph. .	50	109	
Pot. acetate . .	0.4			Zinc sulphate .	0.6	insol	
" bromid . .	1.6	200					

V. S. = very soluble. Sp. = sparingly soluble.

IV. Strength of Watery Solution, in which commonly used salts may safely be prescribed.—(It must be remembered that where several salts are prescribed in the same mixture, the solubility of each is apt to be lowered.)

1. ʒiv *in water* q. s. ℥j: Tannin; Antipyrin; Pot. or Sod. Acet. or Citr.; KI; $AgNO_3$; Na or KBr; Sod. Salicyl; NH_4Cl, $ZnSO_4$, Chloral.
2. ʒiss *in water* q. s. ℥j: Alum, Quin. Bisulph.; $NaHCO_3$.
3. ʒss *in water* q. s. ℥j: $KClO_3$; $Na_{24}BO_7$; Tartar Emetic.
4. *In water* q. s. ℥j:

Acid. Carbolic.	gr. xxv.
Morphinæ S.	gr. xx.
Acid. Boric.	gr. xv.
Strychn. S.	gr. v.
Quin. S.	gr. ss.

V. Solubility in Different Media.—

As a general rule, *inorganic substances* are more soluble in water than in alcohol.

Basic alkaloids are insoluble in water, more soluble in alcohol.

Alkaloidal salts are soluble in either alcohol or water.

Gums are soluble in water, insoluble in alcohol. *Resins* and *essential oils* are the reverse.

(In making mixtures, it must be remembered that spirits, tinctures, and fluid extracts all contain alcohol.)

Glycerin stands intermediate between alcohol and water as a solvent

The following substances are:

1. Practically insoluble in water: Iodin, calomel.

2. Soluble in water, but almost insoluble in alcohol: Alum, NH_4Cl, $KClO_3$, tartar emetic, $ZnSO_4$.

3. Much more soluble in glycerin than in water: Boric acid, alum, carbolic acid, $HgCl_2$.

CHAPTER V.

OUTLINE OF TOXICOLOGIC ANALYSIS.

It is not purposed to give a complete account of the subject in this chapter, for this would require a separate volume or more. Nor is it necessary for any one but a specialist to possess such a knowledge. No one who has not had considerable practice in this class of work should undertake to give testimony which may decide the life of a prisoner. However, every physician should know the general outline of the process employed, so that he may judge the work of others intelligently.

Since the material to be analyzed is usually limited in amount, and cannot be replaced, a toxicologic examination must be arranged in such a way that as many tests as possible may be made successively on the same portion. Consequently, the first operations must be of such a nature as not to interfere with subsequent tests. The symptoms often give a clue to the poison. This does not dispense with a complete examination, but helps to fix the attention on the most likely substance.

If the symptoms have not been of a kind to give definite suspicion of some one substance, the reaction of the sample is to be tested. If this is not markedly acid or alkaline, it is not necessary to search further for corrosive acids or alkalies; and if these are not found in the stomach, it is not necessary to examine other organs for them.

1. Distillation from Acidulated Solution.—The next operation is to distil the liquid after making it faintly acid. The best acid for this purpose is tartaric, using just enough to give a distinctly acid reaction. The principal substances which are to be found in this distillate are: phosphorus, hydrocyanic acid, the various members of the alcohol group, *i. e.*, alcohol, chloroform, ether, chloral, or any of the higher alcohols; the volatile members of the coal-tar series, of which carbolic acid, nitrobenzol, and anilin would have the greatest practical importance. In this distillate might also be found essential oils.

The heat used for this distillation would be destructive to a few poisons, such as toxalbumins, and these would have to be demonstrated in the original liquid by life-tests.

If *phosphorus* is suspected, the method of distillation must be modified, introducing much complication; consequently it is well to test, first of all, by a *preliminary test*, whether phosphorus is absent or may be present. This is done by moistening a strip of filter-paper with silver nitrate, and another with lead acetate.

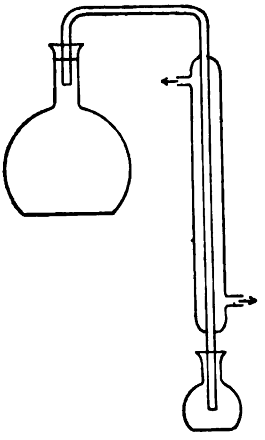

Fig. 44.—Mitscherlich apparatus.

These are to be exposed to the vapors arising from the liquid, by inserting them into a flask at the side of the cork. If this is allowed to stand, even in the cold, the silver paper will turn black in the presence of phosphorus. This can be still further hastened by heating. Of course, phosphorus is not the only substance which blackens silver nitrate paper; consequently the test is only a negative one; that is, if there is no blackening, we may be sure that we have no phosphorus. The lead acetate paper serves to eliminate some of these substances, the principal of which is hydrogen sulphid, for it is blackened by H_2S, but not by phosphorus. If both papers are blackened, the proof is not at all positive that phosphorus is present; but if the silver nitrate paper is blackened, and the lead acetate is not, the probability of phosphorus being present is greater.

The usual method employed in testing for phosphorus is the Mitscherlich apparatus, which consists of a distilling apparatus with an upright condenser (Fig. 44). The acidulated solution is distilled in this apparatus in a darkened room, and if phosphorus is present, a luminous ring is formed in the condenser.

There are, however, quite a number of substances the presence of which interferes with the formation of this ring. Almost any volatile substance may do so: turpentine, chloroform, ether, alcohol; and alcohol is often present, as it is usually given as an antidote.

The absence of the ring does not, therefore, prove the absence of phosphorus. The distillate will contain phosphorus in the lower stages of oxidation, as phosphorous or hypophosphorous acid. The best way to prove phosphorus in this is to treat it with some oxidizing substance, like bromin-water, and then test for phosphoric acid in the ordinary manner:

Evaporate almost to dryness with bromin-water; then apply the test for phosphoric acid, either by magnesia mixture or ammonium molybdate. The phosphorus can also be estimated quantitatively in some such manner, by carrying out the distillation in an atmosphere of carbonic acid, so that the phosphorus cannot be oxidized. The quantitative determination of phosphorus, however, is not at all important; because if it is present at all, it is present as a toxic agent.

The next substance to search for is *hydrocyanic acid.* Hydrocyanic acid is separated by distillation in an ordinary apparatus. Here again a preliminary test is valuable. The most convenient is that with guaiac:

Take some freshly prepared tincture and saturate some filter-paper with this; let it dry somewhat—it need not be perfectly dry; then pour over this some very dilute copper sulphate. With hydrocyanic acid this gives an intense blue color. This is very sensitive; and if this blue color is not obtained, we may be sure there is none present. There are, however, some other substances which give a similar color, but not of exactly the same shade. Ammonia, for instance, will give a rather greenish color,

The best test for hydrocyanic acid in the distillate is the formation of Prussian blue.

To perform this, add a drop of ferric chlorid, and ten drops of ferrous sulphate, to the liquid; then an excess of sodium hydrate. The sodium hydrate, of course, throws down a green precipitate of ferrous hydrate, which must not be taken for Prussian blue; the mixture is heated for a moment and then rendered acid by an excess of hydrochloric acid: if there is a great deal of hydrocyanic acid, there will be a blue precipitate; if only a little, there will be a blue color.

If there is a marked hydrocyanic acid reaction, it is sufficient to show that it is toxic; but if the reaction is slight, one must go further, because it might be present as a result of having eaten almonds or other articles of food from which it could be formed.

In this case it would be necessary to determine the amount present. This is done by means of silver nitrate, which forms a definite compound with hydrocyanic acid and allows its estimation either by volumetric or gravimetric method.

There are a great many other tests for hydrocyanic acid, but these are sufficient. It is not necessary to multiply tests too much until one is fairly sure of the result. Once a substance is isolated, it is well to try all the known tests on it; but while searching for it, one or two are sufficient. Others would be confusing and would use up too much material. With the method which we have given, ferrocyanids might also be decomposed and give rise to hydrocyanic acid; and since ferrocyanids are not toxic, this would lead to wrong conclusions. To eliminate this, the original liquid is filtered and the Prussian blue test applied to it directly. Mercuric cyanid does not yield its hydrocyanic acid in this treatment. If it is suspected, the material must be treated with hydrosulphuric acid before distilling.

Carbolic Acid.—Here also a group reaction is employed first, and one of the most delicate and certain is Millon's reagent. Millon's reagent is added to a sample of the distillate and boiled; if carbolic acid is present, a red color, and if the amount of carbolic acid is large, a red precipitate, results.

Other substances also give Millon's test; for instance, proteids, and in fact, any aromatic substance which contains the group OH.[1] Its presence does not show that carbolic acid is present, but its absence would show that it is not present.

To further determine carbolic acid, the iron test would perhaps be best. Carbolic acid and ferric chlorid give a characteristic violet color. Still another test is the bromin reaction: the addition of bromin-water to a carbolic acid solution causes the deposition of a precipitate of tribromphenol, which has a characteristic microscopic appearance.

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[1] In the proteids, it is supposed to be the tyrosin group which gives Millon's reaction.

This is the most delicate test which we possess for carbolic acid. The proportion must be just right in order to obtain the maximum precipitate; *i. e.*, there must be an excess of bromin-water. The quantitative determination is done by means of a modification of the tribromphenol method.

Another substance of the aromatic series which may be obtained in this manner is *nitrobenzol*, which would be sufficiently characterized by its odor, resembling that of bitter almonds. Nitrobenzol is often used in perfuming soap.

Of the substances of the hydrocarbon series which would be present in this distillate, the most common is *alcohol.*

The stress to be put upon its presence offers some small difficulties because alcohol may be in the stomach without being a poison in the legal sense. It is quite easy to show the presence of even small quantities of alcohol; for instance, by the *iodoform test:* The suspected substance (distillate) is treated with a little sodium hydrate and an excess of Lugol's solution (I + KI). This gives the formation of a precipitate of iodoform and its characteristic odor. About ten times as much iodin is required as alcohol to have a complete precipitation.

Another quite delicate test, not entirely characteristic of alcohol, but given also by other reducing substances, is the reduction of bichromate of potash, or, rather, chromic acid. If bichromate of potash be added to a solution of alcohol, there will be no change; if sulphuric acid is added to the mixture, chromic acid is liberated and is at once reduced, giving rise to a green color (chromous oxid). Heat favors the reaction.

To determine the presence of notable quantities of alcohol a very simple method is sufficient:

The suspected liquid is heated in a flask closed by a stopper carrying an upright tube a meter or so high. The alcohol, having a low boiling-point, will be driven off first. By the use of the long tube, and by carefully regulating the heat, the water may be condensed in such a manner that the alcohol alone leaves the tube at first, and may be ignited. This method is supposed to work with liquids containing 2 to 5 per cent. of alcohol.

The presence of *ether*, if in sufficient quantity to have a toxic action, would be detected by its odor. No further tests would be required. With *chloroform* this would perhaps not be the case, much smaller quantities being sufficient to act toxically, so that it might be well to apply a special test. The resorcin test is one of the best and most delicate. A small amount of resorcin is put in a test-tube with this distillate. Some sodium hydrate is added and the mixture is heated. Chloroform and *chloral hydrate* both give rise to the same reaction—a beautiful red solution. If the distillate is itself odorless, but develops the odor of chloroform on the addition of NaOH, the substance is chloral.

These are practically all the tests that have to be performed on the distillate. The residue remaining in the still is tested for:

2. Fixed Organic Poisons.—This method is treated in detail in experiment II, Chapter XXXIII.

The principle of the method rests upon the solubility of the alkaloids and the insolubility of the alkaloidal salts in ethereal liquids.

The residue of the distillation is evaporated to a small bulk and treated with alcohol in such quantity as to precipitate the proteids and inorganic salts without dissolving the fats. Through the addition of tartaric acid, the alkaloids are converted into salts and pass into the alcohol. The alcoholic solution is again evaporated, and again taken up with water, leaving the fats behind (croton oil).

The filtrate is exhausted with:

1. Sulphuric ether in acid solution, which takes up non-alkaloidal organic poisons.
2. Sulphuric ether in alkaline solution, which takes up most alkaloids.
3. Acetic ether, which takes up the remainder of the alkaloids, and especially morphin.

By taking advantage of the difference of solubility of the different alkaloids in benzol, petroleum-ether, etc., the isolation may be carried still further, but this is not usually necessary, if life tests are used.

The chemic and physiologic reactions of alkaloids may be very closely simulated by ptomains. Such similarity has been found with the following: coniin, colchicin, atropin, delphinin, digitalin, morphin, nicotin, veratrin. The only way to distinguish with certainty between these is to use both the chemic and the physiologic tests. For, as far as is known, there are no ptomains which give both the chemic and physiologic tests of one alkaloid.

When these determinations have been made and have proved negative, all the residues accumulated during the process are put together, the organic matter destroyed, and the residue tested for **fixed inorganic poisons,** according to the methods which are treated of in detail in all text-books on analytic chemistry. It is scarcely necessary to lay stress on the fact that the reagents used must themselves be tested for the poisons. In isolating the alkaloids, ptomains, etc., the ether, etc., must be recently distilled over tartaric acid.

CHAPTER VI.

PRESCRIPTION WRITING; FLAVORING.

(A) PRESCRIPTION WRITING.

General Hints.—The subject of prescription writing seems to possess almost insurmountable difficulties for the student. There is, perhaps, no other subject in the whole course of study which he finds more discouraging and finishes with less satisfaction. Nevertheless the principles upon which it is based are few, simple, and easily memorized. When asked for them, the student usually has no difficulty in answering the questions. The dissatisfaction arises when the student comes to put these principles into practice. But it is the same with any other art: nothing but practice will give expertness. The student who would master this subject must not rest content with doing the few exercises which can be given him in class. As he studies each drug, or as he reads up the treatment of diseases, he should himself compile such prescriptions as the subject suggests. This will not only aid him in prescription writing, but in pharmacology and therapeutics as well. It is only in this way that he can acquire the necessary self-confidence and skill. In our experience, when a class is asked to write a prescription and only the general data are given,—*e. g.*, the disease or the main ingredient,—half the class will give up in despair. A little questioning will bring out the fact that it is not knowledge but method that is wanting. Again, the prescriptions which are handed in for correction are scarcely ever perfect. They betray the fact that the student loses sight of detail. As a help to the student in the recommended home practice, the following rules will be found of value:

When writing a prescription for a given condition, put down, first, the name of the best remedy. Ask yourself whether there is any other drug which may be employed to aid this. Put this down also. Then consider in which form the medicine should be administered, whether as liquid, powder, salve, etc. This will usually determine which preparation of the ingredient is to be employed. Put this down also. Then ask yourself what may be added to render the mixture agreeable to the patient. When this is written down, all the ingredients will be represented. Now look over this carefully and see that there are no incompatibilities and that the constituents are soluble if the mixture is to be a liquid. Next insert the endings. Write the directions to the dispenser. Now consider the doses of the mixture, teaspoonful, tablespoonful, etc., the approximate number of doses, and from these calculate the size of the mixture.[1] It should be considered how many doses are to be taken each day (on the basis of sixteen hours a day); this, multiplied by the number of days, gives approximately the size of the mixture. Then write the directions to the patient. Now consider how much of each ingredient is to be given at each dose, multiply by the number of doses, and write down the quantity. This finishes the prescription. Look over the result carefully in the same order.

It would seem almost superfluous to mention that it is extremely essential in writing prescriptions to use as *legible handwriting* as possible. It is astonishing, in view of the dire results that may follow, how often this self-evident rule is disregarded. The same remarks apply to *abbreviations*. While it is justifiable to employ abbreviations even extensively, it is necessary to make these in such a way that they cannot possibly be misinterpreted. Finally, in his practicing the student should write both the metric and apothecary systems. It is necessary at the present day to be familiar with both, although it is to be hoped that the complicated English system will soon become obsolete.

An efficient aid in acquiring practice in writing prescriptions is to look over a druggists' prescription file, when this may be done.

A prescription may be **defined** as an order for medicine sent by a physician to a pharmacist. Prescriptions may contain the following **parts**:

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[1] Five-ounce (150 c.c.) mixtures are avoided, since there are no bottles of this size on the market.

Heading or Superscription :	℞.	GM.	*vel* c.c.
Inscription : Basis (Ingredients)	Tr. Aconiti	0	45
Adjuvant	Sp. Æther. Nitrosi	15	
Corrective	Liq. Ammon. Acet.	15	
Vehicle	Syr. Simpl.	30	
Subscription (Directions to dispenser) :	Misce		
Signature (" " patient) :	S. Teaspoonful every hour in half a glass of water.		
	Jan. 1. 1901. Dr. N———		
	For Mr. C———		

The prescription is always written in **Latin**, with the exception of the directions to the patient (and to the compounder). This language presents various advantages over English.

In the first place, the names of the drugs are more definite, concise, and unchangeable. There is, as a rule, but one Latin name for each drug, whereas in English the same substance may have several names, or the same name may designate several entirely different substances. Further, it is generally desirable to have the patient ignorant of what medicine he is taking. On the one hand, if he possesses this knowledge he very frequently has preconceived ideas of the action of the medicine, and will either take it in excessive amounts or will neglect to take it entirely, or interfere with its action in some other way. On the other hand, it will encourage the habit of self-medication.

The *directions to the dispenser* are generally written in Latin. There is, however, no necessity and no advantage in this. Usually it is sufficient for this purpose to write simply the letter M (misce) below the inscription.

The *directions to the patient* (signature) are always written in English, so that the patient can read them. The directions should be made as complete as possible, and should include everything which it is necessary for the patient to know. The habit of giving verbal instructions to patients and of having the medicine labeled " use as directed " cannot be too much discouraged. Aside from the fact that human memory is extremely apt to fail, the patient or relatives, when the prescription is given to them, are usually in a more or less excited frame of mind, and cannot be relied upon to remember what is told them. Medicines intended for external application should be plainly labeled to that effect, and when a medicine contains poison, it should be so labeled, except when there is special objection to this.

The *inscription* may consist of but one ingredient. If there are several, they may be classified under the following heading, and then should be placed in the prescription in this order:

Basis: the principal substance.

Adjuvant: the substance which is used to aid the action of the former.

Corrective: whose purpose it is to modify or correct an undesirable action of the basis.

Vehicle: the indifferent substance used to dilute the active ingredients.

Formerly the ingredients of a prescription were almost numberless. This was in the time of empiricism, and was simply an application of the idea that in a large mixture of substances there would probably be one which would do good. This was the so-called "shot-gun prescription." At present the tendency in prescription writing is to make the prescription as simple as possible. This, on the one hand, avoids the chances of incompatibilities, and, what is still more important, makes the action of the medicine more easy to watch and control.

If the prescription includes a number of mixtures, each containing numerous ingredients, such as the numberless preparations now put on the market by many firms, the result is, of course, as much a "shot-gun" prescription as if the prescriber had enumerated all the ingredients.

The copying of a prescription, ingredient for ingredient and dose for dose, is as much empiricism as the use of any other ready-made compound. The physician should be well enough educated to devise his own prescriptions and to obtain such ingredients as will best suit the special needs of the case in hand.

The custom of having prescriptions refilled once or several times obtains in many localities. Whereas it is often impossible for the physician to put a stop to this practice, it is absolutely necessary that he should prevent such prescriptions being refilled which contain narcotics or other drugs likely to cause a habit. He can attain this result by writing "non repetatur" under the prescription. The druggist refilling this will do so on his own responsibility.

When the patient is very poor, it is often customary to invite the druggist to charge him the lowest terms by writing P. P. (Pauperissimus) under the prescription. It is, of course, not just to do this if the physician himself receives a regular fee.

The pharmacist is supposed to check the quantities of the ingredients, and not to dispense a prescription containing an *unusual dose of a powerful poison* without convincing himself that the physician prescribed this intentionally. While this does not in any way lessen the responsibility of the physician, it is a safeguard which deserves all encouragement. To avoid delay, it is customary to mark such large doses in such a way that the pharmacist will have no doubt that they are intentional. Thus: Tr. aconiti, ʒj; or ʒj!; or ʒj Q. R. (quantum rectum), the last being the best.

TABLE IX.—MAXIMUM SINGLE DOSES USUALLY GIVEN OF THE FOLLOWING DRUGS.[1]

To 0.001 Gm. = 1/64 gr.	GM. 0.002–0.005 = GR. 1/30–1/12	GM. 0.006–0.060 = GR. 1/10–1	GM. 0.06–0.3 = GR. 1–5	Above 0.3 Gm. (5 grs.)
		Poisonous Alkaloids.		
Coniin, 0.001 = 1/64 Physostigmin, 0.001 = 1/64	Atropin, 0.002 = 1/30 Nicotin, 0.003 = 1/20 Colchicin, 0.005 = 1/12 Digitalin, 0.005 = 1/12 Veratrin, 0.005 = 1/12 Elaterin, 0.005 = 1/12	Apomorphin, 0.010 = 1/6 Picrotoxin, 0.010 = 1/6 Strychnin, 0.01 = 1/6 Pilocarpin, 0.03 = ½ Morphin, 0.03 = ½ Codein, 0.05 = ¾	Podophyllin, 0.1 = 1½ Narcein, 0.1 = 1½ Santonin, 0.1 = 1½ Brucin, 0.1 = 1½ Caffein, 0.15 = 2 Narcotin, 0.3 = 5	
		Inorganic.		
Phosphorus, 0.001 = 1/64	Arsenious acid and salts, 0.005 = 1/12	$HgCy_2$ 0.02 = ⅓ Hg salts except calomel, Ag salts, Au salts, 0.03 = ½ I, KCy, Br, HCy 2%, 0.05 = ¾ Pb, Zn, and Sn salts, Carbolic, Creosote, 0.06 = 1	Cu salts, 0.1 = 1½ Ba salts, 0.12 = 2 Bi salts, 0.3 = 5 Antim. and pot. tart., 0.2 = 3 Iodoform, 0.3 = 5	$CuSO_4$ or $ZnSO_4$ in divided doses as emetic, Gm. 1.0 = Grs. 15 Chloral, 4.0 = 60
		Organic Drugs.		
		Ol. sinapis, 0.01 = 1/6 Cantharadin, 0.05 = ¾ Croton oil, 0.05 = ¾	Rad. bellad., 0.1 = 1½ Nux vom., 0.1 = 1½ Opium, 0.15 = 2½ Tuber aconiti, 0.15 = 2½ Fol. bellad., 0.2 = 3 Sem. et fol. Stramon., 0.25 = 4 Lactucarium, 0.3 = 5 Rad. veratr., 0.3 = 5 Sem. et fol. Hyoscyami, 0.3 = 5 Fol. digitalis, 0.3 = 5 Gamboge, 0.3 = 5 Colocynth, 0.3 = 5	Ergot, 1.0 = 15

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[1] The ordinary dose is usually one-fifth to one-half of that given.

		Gm. Gr. 0.006–0.060 = 1/10–1	Gm. Gr. 0.06–0.3 = 1.5	Above 0.3 Gm. (5 grs.)
		Solid Galenics.		
		Ext. aconiti rd., 0.02 = ⅓ Ext. physostigmatis, 0.02 = ⅓ Ext. belladonnæ, 0.05 = ¾ Ext. colocynthis, 0.05 = ¾ Ext. nucis vomicæ, 0.05 = ¾	Ext. aconiti fol., 0.1 = 1½ Ext. cannabis ind., 0.1 = 1⅙ Ext. opii, 0.15 = 2½ Ext. conii, 0.18 = 2¾ Ext. digitalis, 0.2 = 3 Ext. hyoscyami, 0.2 = 3	
		Liquid Galenics.		
			Tr. aconiti rd., 0.15 = 2½ Tr. iodin, 0.2 = 3	Liquid arsenic preparations, 0.5 = 7 Tr. nux. vom., 0.5 = 7 Tr. lobelia, 0.5 = 7 Tr. veratrum vir., 0.5 = 7 Tr. belladonnæ, 1.0 = 15 Tr. canthar., 1.0 = 15 Tr. colocynthis, 1.0 = 15 Tr. digitalis, 1.0 = 15 Tr. and vin. colchici, 1.3 = 20 Tr. vin. et. acet. opii, 1.5 = 25 Aq. amygd. amaræ et laurocerasi, 2.0 = 30

Grammatic Construction of Prescriptions.—The heading, inscription, and often the subscription are written in Latin. A slight knowledge of the rules of grammar of this language is therefore essential. It is supposed that this is possessed by the student, and the following is intended merely to recall some of the more important facts:

The superscription, ℞ (recipe: "take thou"), requires the name of the substance to be in the genitive, if the quantity is given, the quantity itself being in the accusative (the latter is, of course, very rarely written out in full). When the quantity is not given, the name of the substance is to be placed in the accusative. Adjectives agree with their nouns in gender, number, and case.

These rules will generally be understood by translating into English: *e. g.*, Take thou of tincture of aconite one ounce.

The following **rules for the formation of the genitive case** will be found valuable (" Mann's Manual "):

RULE 1.—*All nouns ending in* a, *form the genitive in* æ; as Quinina, Quininæ. *Exceptions:* Aspidosperma, Physostigma, and Theobroma form the genitive in atis. Folia is plural; genitive, foliorum.

RULE 2.—*All nouns ending in* us, um, os, on, *form the genitive in* i; as Conium, Conii. *Exceptions:* Rhus, gen. Rhois; Flos, gen. floris; Erigeron, gen. Erigerontis. Fructus, Cornus, Quercus, Spiritus, do not change.

RULE 3.—*All other nouns of whatever termination make the genitive in* s, *or* is. Chloral, gen. Chloralis.

Some lengthen the termination thus:

as,	genitive	atis; as Acetas,	Acetatis.
is,	"	idis; as Anthemis,	Anthemidis.
o,	"	onis; as Pepo,	Peponis.
x,	"	cis; as Cortex,	Corticis.

There are a few exceptions. Asclepias, gen. Asclepiadis; Mas, gen. Maris; Phosphis, Sulphis, etc., gen. itis; Mucilago, gen. Mucilaginis; Solidago, gen. Solidaginis, etc.

The following words do not change in their genitive: Amyl, Azedarach, Berberis, Buchu, Cajuputi, Cannabis, Catechu, Condurango, Cornus, Curare, Cusso, Fructus, Digitalis, Hydrastis, Jaborandi, Kino, Matico, Quercus, Sassafras, Sago, Sinapis, Spiritus.

The **accusative** is rarely employed. It is formed according to the following rules (Mann):

RULE 1.—*Nouns singular ending in* a, *are feminine, and make the accusative singular in* am *and the plural in* as. Example: Drachma, acc. sing. Drachmam, pl. Drachmas.

RULE 2.—*Those ending in* um *or* us, *make the accusative singular in* um. *The accusative plural of those in* us *is* os, *and of those in* um *is* a. Those in *us* are masculine, those in *um* are neuter:

Congius, acc. sing. Congium; acc. pl. Congios.
Granum, acc. sing. Granum; acc. pl. Grana.

Attention is also called to the fact that adjectives change their endings, a fact which the student is apt to forget.

The directions to the dispenser are usually written in Latin, but this is not essential. They should, in every case, be as brief as possible. As a rule, the pharmacist is better informed as to this part than the prescribing physician.

The following *prepositions* are frequently used, and command the following cases:

ad	to	accusative.
ana	of each	genitive.
cum	with	ablative.
in	into	accusative.

The following **Latin words and phrases** occur frequently in prescriptions (abridged from Mann):

TABLE X.

ad	to, up to
ad libitum	at pleasure
adde	add (thou)
ana (ā, āā)	of each
aqua bulliens	boiling water
“ fontana	spring water
“ fervens	hot water
“ destillata	distilled water
bene	well
bis in dies	twice daily
cape, capiat	take, let him take
charta	a paper (medicated)
chartula	a small paper for a powder
cibus	food
cochleare magnum	a tablespoon
“ parvum	a teaspoon
cola, colatus	strain, strained
collyrium	an eye wash
congius (C.)	a gallon
cum	with
dilute, dilutus	dilute (thou), diluted
dimidius	one-half
divide (Div.)	divide (thou)
dividendus	to be divided
dividatur in partes æquales	let it be divided into equal parts
dosis	a dose
extende supra	spread upon
fac, fiat, fiant (ft.)	make, let be made, let them be made
filtra	filter (thou)

gargarisma	a gargle
gutta, guttæ (gtt.)	a drop, drops
haustus	a draught
hora	an hour
in dies	daily
instar	like (with genitive)
lac	milk
libra (lb.)	a Troy pound
mane primo	very early in the morning
magnus	large
misce (M.)	mix
numerus, numero (No.)	a number, in number
octarius (O.)	a pint
ovum,	an egg
pars	a part (governs genitive)
partes æquales (P. æ.)	equal parts
parvus	small
pilula (pil.)	a pill
pro re nata	according to circumstances, occasionally
pulvis	a powder
quantum sufficit (q. s.) (followed by genitive)	as much as is necessary
quaqua hora	every hour
semissis (ss.)	a half
signa	sign
sine	without
si opus sit	if necessary
solve, solutus	dissolve, dissolved
solutio	a solution
statim	immediately
talis	such
tritura	triturate
tere simul	rub together
ter in die	three times a day
vitellus	the yolk (of an egg)

(B) FLAVORING.

I. GENERAL RULES.

The subject of flavoring is one which is very generally neglected by the beginning practitioner, and is one treated very slightly indeed in most text-books on materia medica. It is, however, one of very great importance with the modern patient. Attention to this on the part of manufacturers and the lack of it on the part of physicians is perhaps largely responsible for the increased use of proprietary medicines. Patients very often will fail to take a disagreeable medicine, and the physician should always be on the lookout for such cases. It is scarcely necessary to say that he should approximately control the amount taken by judging as to the quantity left in the container, as he should also, in general, control the medicine dispensed by the druggist as to its appearance and taste.

Some patients will carry the deceit somewhat further and pour away the appropriate amount of the medicine, and if the physician does not obtain the anticipated results, it may be well to administer some test medicine to the patient without his knowledge. This may be done by giving him a prescription for salol (5 grains); if he takes this, it can readily be discovered in the urine by the addition of strong sulphuric acid and a few drops of ferric chlorid, which will give a violet color. The same object may be accomplished by potassium iodid, which can be tested for by adding to the urine a few drops of HNO_3 and a little chloroform. The latter becomes a violet color.

The subject of flavors is not only important because it humors the patient, but when the flavoring is properly done it has an advantageous action in the treatment of the disease. It puts the patient in more favorable condition for the action of the drug, aiding absorption and digestion. One need only point to the value of condiments in food. It is rather surprising that a physician who would object very strongly to eating his food without seasoning will prescribe medicine without giving a thought to this subject.

Condensed Rules.—The substances which may be used for improving the taste of a mixture are almost without number. Before proceeding to a detailed discussion, we shall give in a condensed form those methods which are apt to be most useful. The quantities need not necessarily be specified, it being sufficient to mark them "q. s."

Appearance.—Liquid prescriptions intended for internal administration should be clear if possible. It might be well to mark all such prescriptions "filtra." The appearance may be very materially improved by the addition of some coloring-matter, and this may also prove useful through its suggestive element and by hiding the nature of the medicine from the patient. The following are recommended for *solutions* in the proportion of about 2 drops to the ounce (0.4 : 100):

Red: * Tinctura Persionis N.F.
Brown: * Tinctura Persionis Composita N.F.
Yellow: * Tinctura Curcumæ N.F.

* Not official.

For *powders*, Carmine.

For **improving the taste** for children, Syrupus Tolutanus; for *adults*, Elixir Aromaticum. This is further improved by the addition of 2 grains of citric acid to the ounce (0.4 : 100).

For the administration of *salts*, where the alcoholic elixirs are not admissible, use Aqua Menthæ Piperitæ or 2 grains citric acid per ounce.

For *emulsions*, 6 drops Spiritus Aurantii Compositus per ounce; other flavoring spirits are used in the same proportion.

For producing a *bitter* flavor use Elixir Gentianæ N.F.

To render the administration of a great amount of *hot water* acceptable, use decoction of Species Pectorales N.F. in the proportion of 2 tablespoonfuls to the cup.

For the administration of *cold water* use lemonade.

For the flavoring of *cough medicines* use Syrupus Glycyrrhizæ.

II. COLORING.

Anilin colors should be avoided as far as possible, since they are frequently more or less toxic.

1. Watery or Alcoholic Liquids.

The following are especially useful in slightly acid liquids. The tinctures are used in the proportion of 2 drops to the ounce (0.4 : 100).

(*A*) *To produce a red color:*

* *Tr. Persionis* N.F., prepared from a lichen—12½%—one-third alcohol—miscible with alcohol and water.

U.S.P. *Syrupus Rubi Idæi* U.S.P.—raspberry juice, preserved with sugar.

(*B*) *To produce a reddish-brown color:*

* *Tr. Persionis Comp.* N.F.—2% persionis, 10% caramel—miscible with water and alcohol.

(*C*) *To produce a yellow color:*

* *Tr. Curcumæ* N.F. (Curcuma longa, Turmeric, Zingiberaceæ, Southern Asia)—15%, alcohol, miscible with alcohol, but not with water. If the mixture is aqueous, it must be filtered. Alkalies will change the color to reddish-brown.

Crocus, Saffron (Stigmata of Crocus sativus, Irideæ, cultivated in Spain and France).

It also contains volatile oil and is used popularly as a carminative and emmenagog.

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* Not official.

Tr. Croci B.P., U.S.P.—10%—one-half alcohol—miscible with water and alcohol.

(*D*) *To produce a brown color:*

Caramel—partly carbonized starch—sugar.

(*E*) *For other colors*, anilin dyes must be used.
For blue, methylene-blue.
For violet, gentian-violet.

2. Oily Liquids.

(A) **Red:** * *Alkanet*—root of Alkanna tinctorea, Boragineæ—West Asia.

(Red with acids; blue with alkalies.)

* *Madder:* Wood of Rubia tinctorum, Rubiaceæ. Levant and Southern Europe. Contains especially alizarin and other coloring-matters. Little soluble in water.

(B) **Yellow:** * *Annatto*—pulp surrounding seeds of Bixa orallana, Bixineæ—South America—insoluble in water—soluble in alcohol, ether, and oil.

(Frequently used for coloring butter.)

3. Powders.

(A) **Red:** * *Carmine*—a precipitate obtained from decoction of cochineal by alum or cream of tartar. Soluble in alkalies, brightened and precipitated by acids. Also soluble in alcohol. Contains carminic acid. May also be used for coloring liquids: * *Liquor Carmini* N.F. 6%, with ammonia and one-third glycerin.

Cochineal U.S.P.—females of the insect Coccus cacti—Mexico and Central America.

Iron oxid or *carbonate.*

* *Armenian bole* is an iron-containing clay used for this purpose.

(B) **Blue:** * *Ultramarine*—compound of aluminium and sodium silicate and sodium polysulphid. It is insoluble.

* *Litmus*, a pigment obtained from lichens. Insoluble in alcohol, soluble in water.

* *Indigo*, a pigment obtainable from a number of plants and also synthetically. The active principle is a colorless glucosid, plant indican. Under the action of ferments or acids it yields indigo-blue or indigotin. This is insoluble in ordinary solvents, but dissolves in concentrated H_2SO_4. If this solution is neutralized with NaOH, the pigment remains in solution and produces a beautiful blue color, which is, however, destroyed by oxidizing or reducing agents.

(C) **Black:** * Lampblack or soot (fuligo ligni).

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* Not official.

III. DISGUISING THE TASTE IN SOLID FORM.

This may be accomplished by administering the substance in the form of pills, triturates, capsules, cachets, tablets, etc. In the case of the ordinary pills or tablets, there is generally some taste before they can be swallowed, and this is obviated by coating them with gelatin, sugar, chocolate, etc. All these measures diminish the solubility of the substance, the most, perhaps, in the case of pills. Triturates or compressed tablets can be prepared so as to disintegrate and dissolve as easily as the powder itself. However, most of the preparations put out by the manufacturers do not conform to this demand, and probably all harden on keeping.

IV. MEASURES FOR DESTROYING THE TASTE.

Certain substances have the property of paralyzing the sensory endings of taste. Among these is Yerba santa. (See Chap. X.) This destroys the taste for bitter substances especially. It is, however, therapeutically objectionable. It probably renders alkaloids insoluble, and as for ordinary bitters, it is extremely probable that the therapeutic action is connected with the bitter taste. One c.c. of the fluid extract covers the taste of 0.012 Gm. of quinin sulphate or 1.5 Gm. of quassia.

Similar properties are found in the following plants:

* Gymnema sylvestre,—Africa.
* Bulmenia dulcifica,—Sudan.
* Phrynium Danielli,—West Africa.

The same object, the rendering tasteless of the substance, may be accomplished by rendering it insoluble in the saliva. This can be accomplished with a number of alkaloids by the addition of tannin. Unfortunately this almost invariably diminishes the solubility in the lower portions of the alimentary canal as well.

V. DEMULCENTS.

(See also Chap. XXXI, A.)

Demulcents may be defined as non-absorbable, slimy, colloid substances, generally soluble in water and insoluble in alcohol. They very markedly diminish the characteristic taste of all substances, acid, salt, and sweet, as well as bitter.

* Not official.

They do this by enveloping the substance and forming a protective layer over the mucous membrane, and in this way preventing the access of the substance to the taste organs. This, of course, diminishes absorption as well as taste. One can very readily convince himself of this "corrective" action by mixing a 1% solution of citric acid with water and with a thin starch paste. The latter will taste very much less sour. Colloid substances of this kind are present in fruits as pectin bodies, and have a very marked influence upon their taste. The raspberry, for instance, actually contains more acid than the currant and but little more sugar, its less sour taste being due to the greater amount of these pectin substances present in it.

Materia Medica of Demulcents.

⁂ **Acacia,** U.S.P. (*Acaciæ gummi*, B.P.)—*Gum Arabic.*—A gummy exudation of Acacia senegal and other species of Acacia. Africa. Soluble in water, precipitated by alcohol.

⁂ *Mucilago Acaciæ.* Dose ad libitum.

⁂ *Syrupus Acaciæ* (U.S.P.). Dose ad libitum. (Mucilage, 1; simple syrup, 3.)

Tragacantha.—*Tragacanth.*—A gummy exudation from Astragalus gummifer and other species. Asia Minor. Forms paste with hot water.

Mucilago Tragacanthæ.

Pulvis Tragacanthæ Compositus, B.P.

Cetraria, U.S.P.—*Iceland Moss.*—A lichen, Cetraria islandica. Iceland and Norway. Also contains a bitter principle, which can be extracted by cold water. Boiled with water after previous maceration with cold water, it yields a jelly (decoctum cetrariæ, 5%).

Decoctum cetrariæ, U.S.P.

Chondrus, U.S.P.—*Irish Moss* (Carrageen).—The seaweeds Chondrus crispus and Gigartina mammillosa. Iceland and North America. Yields jelly with boiling water.

Ulmus, U.S.P.—*Slippery Elm.*—Inner bark of Ulmus fulva, Urticaceæ. North America. Used as decoction (and poultice).

Mucilago Ulmi, U.S.P.

Linum.—*Linseed.*—*Flaxseed.*—Seed of Linum usitatissimum, Lineæ; cultivated. Mucilage and fixed oil. Used as demulcent in the form of decoction made from the whole seed. The meal is used in poultices and the oil like other bland fixed oils.

Linum contusum, B.P., crushed linseed.

Amylum.—*Starch.*—The official is the corn-starch, but the other starches act similarly. They are also used as nutrients. Arrowroot is often given for the latter purpose. They are boiled with water; the flour may also be used, but is not as smooth:

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* Not official.

The most important preparations are marked ⁂.

Amylum (Maidis) = corn-starch.
" Tritici = wheat starch.
" Oryzæ = rice starch.

Tapioca, Sago, etc., belong rather to the nutrients.

Oatmeal porridge is a convenient way of administering pills or powders, these being placed in the center of some of the porridge in a spoon.

Other demulcents, not quite as often used for this purpose, are the following. They are all used as decoctions:

* *Salep.*—The tuber of various species of Orchis; contains gum and starch.

Althæa, U.S.P.—*Marshmallow.*—The root of Althæa officinalis, Malvaceæ. Gum and starch.

Syrupus Althææ, U.S.P.

* **Malva.**—Leaves and flowers of Malva silvestris and vulgaris, Malvaceæ. Gum and starch.

* **Verbascum.**—*Mullein.*—Flowers of Verbascum thapsiforme, Scrophulariaceæ. Gums.

* **Cydonia.**—*Quince.*—Seed of Cydonia vulgaris, Pomaceæ. Gums.

Mucilago cydoniæ.

Gelatina, B.P.—*Ichthyocolla* (Isinglass), etc. Various jellies may be found useful, especially in giving pills to children.

* **Dextrinum.**—*Dextrin.*—Prepared by heating starch with nitric acid. Presents all the characters of gum arabic, and forms the principal ingredient of *commercial mucilages.* A good formula for this is the following (Sykes): Mix 180 Gm. of dextrin with 180 c.c. cold water; add 240 c.c. boiling water and boil five minutes, stirring constantly. Add hot water q. s. 400 c.c. When cold, add 30 c.c. dilute acetic acid, 10 drops carbolic acid, and 30 c.c of glycerin, previously mixed.

VI. SWEET SUBSTANCES.

The basis of most of these is sugar—**Saccharum,** U.S.P. (Saccharum purificatum, B.P.)—used in the granulated form (beet- or cane-sugar may be used indifferently). It is very widely distributed in the vegetable kingdom. Soluble in 0.5 parts of water or 175 parts alcohol.

⁂ *Syrupus.*—85 Gm. in 100 c.c.; made by heat or percolation.

The simple syrup should be but rarely used, the flavored preparations S. Aurantii, S. Tolutanus, and especially the Elixir being preferred.

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* Not official.

The most important preparations are marked ⁂.

Honey (Mel Despumatum) is also a very pleasant flavor when fresh and pure.

Of semi-solid preparations, the thicker are called *confections* (Confectio Rosæ). Powders may be incorporated in these, but they are largely obsolete. Somewhat thinner preparations were called *electuaries*.

Lump-sugar is useful for administering liquids given in drop doses. When flavored with an essential oil, it is called *eleosaccharum*.

Maple-sugar—the evaporated sap of Acer saccharinum, Aceraceæ, North America—may be looked upon as a natural eleosaccharum.

⁂ *Saccharum Lactis, milk-sugar*, prepared by evaporating and crystallizing the whey of cows' milk, is often used as a diluent for powders, its hardness facilitating comminution by intervention (see p. 47). It is soluble in 6 parts of water.

Manna, U. S..P.—the hardened sap of Fraxinus ornus, Oleaceæ, Mediterranean—contains principally mannit. It is used as a laxative, scarcely ever as a flavor.

In cases where sweetening is desired and sugar is excluded, particularly in cases of diabetes, the artificial synthetic product *saccharin* may be substituted. It is about three hundred times as sweet as sugar, but the taste is not exactly the same. The dose for a cup of coffee or tea is about one-half to one grain. *Glycerin* is another sweetening substance which does not contain sugar, and is sometimes employed in place of saccharin. A principle of quite a different kind is the principle of *glycyrrhiza*. This acts only in alkaline liquids, especially ammoniacal. It has no effect if the liquid is made acid.

⁂ *Saccharin* (*Glusidum*, B.P.).—Soluble in 230 water or 30 alcohol. It is believed by some that its long-continued use may give rise to nephritis.

* *Dulcinum*, another synthetic product, is less soluble in water.

⁂ *Glycerinum*.—Prepared by the decomposition of fats and distillation. Should be colorless, oily, soluble in water or alcohol, insoluble in ether, oils, etc.

Its uses as a solvent, preservative, and emollient are discussed elsewhere. It is not of much use as a flavor, since its taste is rather disagreeable to most people.

Glycyrrhiza, U.S.P. (*Glycyrrhizæ radix*, B.P.).—*Licorice*.—Root of Glycyrrhiza glabra, Leguminosæ. Southern Europe and western Asia. Its taste is especially agreeable to children; less so to adults. It is also demulcent.

* Not official.

The most important preparations are marked ⁂.

Glycyrrhizin (a glucosid, the ammonium salt of which causes the taste); sugar, starch.

Preparations:

Extractum G.—The watery extract evaporated to a solid consistency (and usually formed into rolls). Soluble in water.

*** *Extractum G. fluidum.*—One-third alcohol and 5% ammonia water. Miscible with water and alcohol. Dose ad libitum.

* *Syrupus G.*, N.F.

*** *Elixir G.*, N.F., *Elixir G. aromaticum.*—Twelve per cent. of solid extract.

Glycyrrhizinum Ammoniatum, U.S.P.—Prepared by precipitating an aqueous alkaline extract by sulphuric acid, dissolving in ammonia, and evaporating the solution. Soluble in water or alcohol. It possesses no advantage over the extract, and is devoid of the demulcent properties. Dose, 0.3 to 0.6 Gm. (5 to 10 grains).

Other sugars—glucose, molasses, manna, maltose, etc.—are of small importance as flavors.

* **Glucose.**—Prepared by acting on corn-starch with hot dilute sulphuric acid, and found in commerce either as a syrup or in solid masses. It is not as sweet as sugar, and generally contains dextrin, which makes it less easily absorbed. It is less soluble than cane-sugar in water, but more so in alcohol.

VII. FLAVORS PROPER.

These consist for the most part of essential oils, acting at once upon the organs of taste and smell. Sometimes, however, other solid principles form the flavoring principle.

Essential oils act partly as reflex stimulants, and in that connection they will again be considered in Chapter XXIX. They consist of a solid and a liquid portion (stearoptene and eleoptene), the latter being the stronger. They are soluble in alcohol and in ether, and only to an extremely small extent in water, but sufficiently so to impart their flavor to it.

These oils are prepared by distillation *per se*, with water, or by expression, or by solution with appropriate solvents, or by absorbing them with fixed oils. They are preferred to preparations made directly from the drug, since they are free from other extractive material. The essential oils lose their flavors very readily on keeping through the development of ozone, etc. Their keeping quality may be very much improved by adding to them three volumes of alcohol and using a correspondingly larger amount in the preparations. They may be divided into sweetish and aromatic flavors. To these may be added the acid flavors belonging to miscellaneous groups having other therapeutic qualities.

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* Not official.

The most important preparations are marked ***.

Table of Materia Medica of Plants Containing Odorous Flavoring Principles.

(A) Sweet Flavors.

I. Rose Flavors.

NAME.	FAMILY.	HABITAT.	ACTIVE PRINCIPLE.
[1] *Rosa damascena* . . .	Rosaceæ.	Southern Europe and Turkey; cultivated.	Oil of rose (ottar of rose.)
" (other species) .	"	Cultivated.	Volatile oil.
[2] *Fruits*	"	"	Volatile oils and ethers.
* *Pelargonium*	Geraniaceæ.	"	Oil of rose geranium.
* *Andropogon nardus* . .	Graminea.	East India.	Oil of lemon grass.
* " *Schoenanthus* .	"	" "	Oil of Indian geranium.
* *Rosmarinus officinalis.*	Labiatæ.	Cultivated.	Oil of rosemary.

II. Other Flowers.

(Often including the plant.)

NAME.	FAMILY.	HABITAT.	PART USED.	ACTIVE PRINCIPLE.
Lavandula vera .	Labiatæ.	Southern Europe; cultivated.	Flowers.	Oil of lavender.
Melissa officinalis .	"	Southern Europe; cultivated.	Plant.	Oil of balm. Bitter principle.
* *Monarda punctata.*	"	North America.	"	Oil.
* *Trifolium* (species).	Leguminosæ.	"	"	"
* *Melilotus officinalis.*	"	"	"	"
* *Citrus aurantium* .	Rutaceæ.	Cultivated.	Flowers.	Oil of Orange flowers (oil of neroli).
* *Spiræa tomentosa* .	Rosaceæ.	North America.	Plant.	Oil.
[4] * *Iris florentina* . .	Irideæ.	Northern Italy; cultivated.	Root.	Oil and bitter principle.
Anthemis nobilis .	Compositæ.	Temperate zone.	Chamomile flowers.	Oil. Bitter.
Sambucus (species)	Caprifoliaceæ.	"	Elder flowers.	Oil. Gum.
* *Tilia* (species) . .	Tiliaceæ.	"	Linden flowers.	" Gum.
Salvia officinalis .	Labiatæ.	"	Sage herb.	" Tannin.

[1] Rose Oil: The eleoptene is the most valuable part.

[2] The greater number of the common fruits are obtained from plants of the family of Rosaceæ. Fruit jellys are useful to disguise the taste of pills, etc.

[4] * IRIS. Other species of iris may be used similarly, and are especially employed for flavoring powders.

* Not official.

III. Solid Odorous Principles.

NAME.	FRUIT.	FAMILY.	HABITAT.	PART USED.	ACTIVE PRINCIPLE.
[3] *Vanilla planifolia.*	Vanilla bean.	Orchidaceæ.	Central America.	Fruit.	Vanillin.
[4] * *Dipterix odorata* .	Tonka bean.	Leguminosæ.	Guiana.	Fruit.	Coumarin.

IV. Odorous Resins (Balsams and Gum-resins).

These usually contain benzoic or cinnamomic acid with volatile oils. They are slightly antiseptic and locally stimulant.

1. GUM-RESINS (emulsifying when rubbed with water):

NAME.	SOURCE.	FAMILY.	HABITAT.
Galbanum . .	Ferula Galbanum.	Umbelliferæ.	Persia.
Ammoniacum .	Dorema Ammoniacum.	"	"
Olibanum . . (Frankincense)	Boswellia.	Burseraceæ.	Africa and Arabia.
Myrrha . . .	Commiphora Myrrha.	"	" " "

2. BALSAMIC RESINS (insoluble in water, soluble in alcohol or ether):

NAME.	SOURCE.	FAMILY.	HABITAT.
Benzoinum .	Styrax benzoin.	Styraceæ.	Sumatra and Java.
Balsamum peruvianum	Toluifera pereiræ.	Leguminosæ.	Central America.
Balsamum tolutanum	" balsamum.	"	Venezuela.
Liquidamber (Sweet gum)	Liquidamber styraciflua.	Hamamelideæ.	North and Central America.
Styrax . . .	" orientalis.	"	Asia Minor.
* *Populus* . . (Balm of Gilead)	Poplar buds are covered with a balsamic resin.		

V. Musk Flavors.[5]

Moschus. *Castoreum.* *Sumbul.*

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[3] VANILLA. The flavor is much improved by a fermentation to which it is subjected. The flavoring principle is *Vanillin*, an aldehyd, which can also be obtained synthetically.

[4] Vanilla flavoring is often falsified with *tonka bean*.

[5] MUSK FLAVORS. The products were formerly all obtained from the animal kingdom, but some are now made synthetically. The principal is—

MOSCHUS, musk, the dried secretion of the preputial follicles of Moschus moschiferus, Thibet and China.

The odor of the tincture improves on keeping. Also possesses in high degree the property, common to all odorous oils, of reflexly stimulating the medulla.

Some other animals yield similar products which are used in perfuming, but are of no importance in medicine. The same holds true of the synthetic substitutes.

Amongst plants, the Sumbul also shows a similar odor.

* CASTOREUM. From the preputial follicles of Castor fiber.

* Not official.

(B) Aromatic Flavors.

I. Orange Flavors.

The volatile oil is contained in large cells of the rind of the fruit. The plants all belong to the family Rutaceæ, and are cultivated along the Mediterranean and in Florida and California. Citrus vulgaris also contains a bitter principle.

NAME.	PRODUCT.
Citrus vulgaris.	Oleum Aurantii Amari.
" *Aurantium.*	" " dulcis.
" *Limonum.*	" Limonis.
" *Bergamia.*	" Bergamottæ.

II. Menthol and Similar Flavors.

The stearoptene of the oil is menthol or thymol. The whole plant is used.

NAME.	COMMON NAME.	FAMILY.	HABITAT.
Mentha piperita	Peppermint.	Labiatæ.	North America, etc.
" *viridis*	Spearmint.	"	" " "
" (other species)			
* *Thymus vulgaris* . . .	Thyme.	Labiatæ.	Cultivated.

III. Flavors from Umbelliferæ.

The oils are contained principally in the seed or root. The plant grow in temperate climates and are largely cultivated.

SEEDS:	*Carum Carvi.*	Caraway.
	* " *Petroselinum.*	Parsley.
	* *Apium graveolens.*	Celery.
	Pimpinella Anisum.	Anise.
	Anethum Fœniculum.	Fennel.
	* " *graveolens.*	Dill.
	Coriandrum sativum.	Coriander.
	* *Daucus Carota.*	Carrot.
	* *Cuminum Cyminum.*	Cumin.
ROOTS:	* *Angelica purpurea.*	Angelica.
	* *Archangelica officinalis.*	"
	* *Osmorrhiza longistylis.*	Sweet Cicely.

Illicium verum (star anise, family Magnoliaceæ) resembles anise greatly in flavor; other genera of the family (Magnolia acuminata) also possess very aromatic fruits.

IV. Other Sweet Aromatics.

NAME.	COMMON NAME.	FAMILY.	HABITAT.	PART USED.
Sassafras officinalis.		Lauraceæ.	North America.	Root bark (other portions of the plant also contain the oil).
Acorus Calamus .	Sweet flag.	Araceæ.	North America.	Root.
Aralia quinquefolia	Ginseng.	Araliaceæ.	"	"
(Other species also contain similar principles. This drug is highly valued by the Chinese.)				
* *Trigonella Fœnum Græcum* . . .	Fenugreek.	Leguminosæ.	India, Mediterranean; cultivated.	Seeds.

* Not official.

V. Pungent Volatile Oils and Resins.

NAME.	COMMON NAME.	FAMILY.	HABITAT.	PART USED.
[6] *Gaultheria procumbens*	Wintergreen.	Ericaceæ.	North America.	Herb.
Caryophyllum	Cloves. Unexpanded flowers of Eugenia caryophyllata.	Myrtaceæ.	Tropics; cultivated.	
Pimenta officinalis	Allspice.	Myrtaceæ.	Tropical America; cultivated.	Fruit.
Cinnamomum (Cassia or Zeylanicum.)		Lauraceæ.	China or Ceylon.	Bark.
Myristica fragrans	Nutmeg (Myristica)=seed; mace (macis)=seed envelope (arillode).	Myristicaceæ.	Cultivated in tropical countries.	
Piper nigrum.	Black pepper.	Piperaceæ.	India; cultivated in tropics.	Unripe seed.
(Piper album is the above peeled.)				
Elettaria Cardamomum.	Cardamon.	Zingiberaceæ.	India; cultivated.	Fruit.
[7] *Zingiber officinale.*	Ginger.	Zingiberaceæ.	Tropics; cultivated.	Rhizome.
* *Asarum canadense.*	Wild ginger.	Aristolochiaceæ.	North America.	Root.
Capsicum fastigiatum.	Red pepper.	Solanaceæ.	Cultivated in tropical countries.	Fruit.

VI. Hydrocyanic Acid Flavors.

These are contained in the kernels, leaves, and bark of many plants of the rose family.

Of some importance are:

Amygdala amara (U.S.P.). *Bitter almonds.* The seeds of Amyg. Am., family Amygdalaceæ. Cultivated. The oil is chiefly benzaldehyd, C_7H_6O with HCN. *Nitrobenzol* has a very similar odor.

Prunus serotina. Wild cherry bark. (Tannin.)

Prunus laurocerasus (B.P.). Cherry laurel leaves.

(C) Preparations of the Foregoing.

All the plants may be used in the form of *decoction* or *infusion*, employing the usual strength of 1 : 20.

1. *Volatile Oils*, official. Used for flavoring in proportion of 1 drop to the ounce (0.2 : 100), but *only in alcoholic liquids* (they should be preserved diluted with 3 volumes of alcohol):

Oleum Amygdalæ Amaræ, U.S.P.
Anethi, B.P.
Anisi, B.P., U.S.P.
Anthemidis, B.P.
Aurantii Corticis, U.S.P.
" Florum, U.S.P.
Oleum Bergamottæ, U.S.P.
Betulæ Volatilis, U.S.P.
Carui, U.S.P., B.P.
Caryophylli, U.S.P., B.P.
Cinnamomi, U.S.P., B.P.
Coriandri, U.S.P., B.P.

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[6] The oil is methyl salicylate, and in larger doses shares the therapeutic properties of salicylic acid.

[7] Several varieties are on the market. Besides the volatile oil, it contains resin, starch, and mucilage.

* Not official.

Oleum Fœniculi, U.S.P.
Gaultheriæ, U.S.P.
Lavandulæ Florum, U.S.P., B.P.
Limonis, U.S.P., B.P.
Menthæ Piperitæ, U.S.P., B.P.
" Viridis, U.S.P., B.P.
Oleum Myrciæ, U.S.P.
Myristicæ, U.S.P., B.P.
Pimentæ, U.S.P., B.P.
Rosæ, U.S.P., B.P.
Rosmarini, U.S.P., B.P.
Sassafras, U.S.P.
Thymi, U.S.P.

2. *Oleoresina.* (Not used for flavoring; strongly irritant.)
3. *Aquæ.* (Dose of the flavoring waters is ad libitum.)

(Official in both Pharmacopœias.)

Aqua Amygdalæ Amaræ.
⁂ *Anisi.*
⁂ *Aurantii Florum.*
" " Fortior.
Cinnamomi.
Aqua Fœniculi.
⁂ *Menthæ* Piperitæ.
" Viridis.
⁂ Rosæ.
" Fortior.

4. *Spirits.* (Only miscible with alcoholic liquids; for flavoring, 10 drops to ℥, 2 : 100.)

The following are official in the U.S.P.:

Spiritus Amygdalæ Amaræ.
Anisi (also B.P.).
Aurantii.
⁂ " *Compositus* (blended aromatics).
Cinnamomi (also B.P.).
Gaultheriæ.
Spiritus Lavandulæ (also B.P.).
Limonis.
Mentha Piperitæ (also B.P.).
" Viridis.
Myrciæ.
Myristicæ (also B.P.).

National Formulary:
Spiritus Cardamomi Compositus.

5. *Elixirs.* Miscible with water and alcohol. The aromatics are blended in the proper proportions. Dose ad libitum. The following are purely for flavoring:

Official:
⁂ *Elixir Aromaticum.*

National Formulary:
Elixir Adjuvans (contains licorice).
⁂ *Anisi* (anise cordial).
Curassao.
Elixir Gentianæ.[1]
⁂ *Glycyrrhizæ.*

6. *Tinctures.* Dose, 10 drops to ℥ (1 : 100).

Official in U.S.P.:[2]

	%	MENSTRUUM = ALCOHOL.	MISCIBLE WITH:
Tinctura Moschi	5	½	Alcohol and water.
Cinnamomi	10	¼	" " "
⁂ *Gentianæ co.*	10	⅔	" " " (aromatics).
Tolutana	10	1/1	Alcohol.
⁂ *Vanillæ*	10	⅔	" and water.
Benzoini	20	1/1	"
Aurantii Amar.	20	⅔	"
" Dulc. (B.P.)	20	1	"
Myrrhæ	20	1	"
⁂ *Zingiberis* (B.P.)	20	1	" and water.
Lavandulæ Comp. (B.P.)		¼	" " "
Cardamomi Comp. (B.P.)		½	" " "

[1] This is detannated and may be used where iron is to be administered in combination with a bitter.

[2] Those marked (B.P.) are also official in the British Pharmacopœia.
The most important preparations are marked ⁂.

National Formulary:
⁂ Tinctura Aromatica.

7. *Syrups.*[1] Dose ad libitum.
Official in U.S.P.:
Syrupus Acidi Citrici.
  Amygdalæ.
  Aromaticus (B.P.).
⁂ Aurantii (B.P.).
  " Florum (B.P.).
  Limonis (B.P.).
  Picis Liquidæ.
Syrupus Pruni Virginianæ (B.P.).
  Rosæ (B.P.).
  Rubi Idæi.
  Sarsaparillæ Comp.
⁂ Tolutanus.
  Zingiberis (B.P.).

National Formulary:
Syrupus Coffeæ.
  Cinnamomi.
⁂ Syrupus *Glycyrrhizæ.*

8. *Honeys.*
Official:
Mel Rosæ, U.S.P. Boracis; Oxymel.; Oxymel Scillæ, B.P.

9. *Confections.*
Official:
Confectio Rosæ, U.S.P. Piperis, Rosæ Gallicæ, Sennæ, Sulphuris, B.P.

10. *Species.*
National Formulary:
⁂ *Species pectorales:* contains Althæa, Tussilago, Glycyrrhiza, Anise, Mullein, Orris. Infusion made 1 : 10. Dose, teacup.

(D) Acid Flavors.

These are among the most useful for disguising an unpleasant taste. They also aid in dissolving such substances as alkaloids, and assist the absorption of liquids.

A larger amount of cold water can be taken and disposed of when it is used in the form of lemonade or as soda-water—*i.e.*, water saturated with CO_2. The latter acid and organic acids, especially citric, are the most useful. The mineral acids should not be employed, since they are liable to cause gastritis if their use is continued. *Carbonic acid* is useful especially for the administration of salts, and is most conveniently used in the form of granular effervescent salts. *Citric acid* is used in the proportion of 2 grains to the ounce (0.4 : 100), or it may be employed in the form of Syrupus Acidi Citrici (1%, flavored with lemon). *Tartaric acid* may be used in the same proportion.

(E) Miscellaneous Flavors belonging to Other Groups.

1. *Caffein Flavors.*—These, as well as the beef-extracts, are discussed in Chapter VIII (B).
2. *Alcohol Flavors.*—Discussed in Chapter XIX (B).

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[1] Those marked (B.P.) are also official in the British Pharmacopœia. The most important preparations are marked ⁂.

3. *Bitter Flavors.*—These are especially agreeable to men and disagreeable to women and children. The active part are alkaloids, glucosids, or other unclassified "bitter principles." They are most often given for their physiologic effect and will receive more extended notice in Chapter XXX (A). As flavors, they are best combined with strong aromatics.

PART II.

PHARMACOLOGY, THERAPEUTICS, AND MATERIA MEDICA.

CHAPTER VII.

INTRODUCTION TO PHARMACOLOGY; HISTORY OF THERAPEUTICS.

(A) INTRODUCTION TO PHARMACOLOGY.

1. **Scope.**—In its widest sense, pharmacology signifies *all* knowledge pertaining to drugs, and in this sense its meaning is almost as comprehensive as that of "science." It includes materia medica, chemistry, zoology, botany, pharmacy, therapeutics, physiology, pathology—in fact, all the subjects forming the medical curriculum and some others besides; subjects which are taught elsewhere, and which it is, of course, impossible to take up here, although excursions may be made into their field when this appears profitable.

It would be very difficult for the student to understand general principles until he is in possession of a sufficient quantity of facts and details on which to base them. It would, therefore, be a great loss of time to begin with a thorough discussion of the principles and to take up the details later. On the other hand, it would be equally difficult to first study all the details and later deduce the principles. The proper way is, to carry on the two at once. But it is plain that the more details and facts we have mastered, the better can we group them; and as the details constitute the dry facts of science and the generalizations the more interesting parts, so it must be expected that the subject seems at first dry, uninteresting, and unpractical. But the more faithfully one has worked his way through this period, the richer will be the reward in the end, the better the understanding of the subject.

2. **Definition and Relations.—Pharmacology** (sometimes called *experimental therapeutics* or *pharmacodynamics*), in its modern meaning, treats of the action of chemic substances on living tissues—of the changes produced in the structure, composition, and function of living bodies by unorganized, chemically acting substances, not belonging to their normal environment.[1] Pharmacology therefore goes

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[1] Physicochemic phenomena like osmosis and solution are included in the term "chemic action" in this definition.

a step further than what used to be called the "physiologic action," in that it aims to furnish the *explanation* for the changes observed.

The allied sciences, **materia medica** and **pharmacognosy**, treat of the history, appearance, and physical and chemic characters and doses of these substances; **pharmacy** of their preparation; **therapeutics** of their application in the treatment of disease. **Toxicology** treats of those substances which are particularly apt to occasion deleterious effects.

In the strict limits of the definition, pharmacology is only one branch of biology. It treats simply of a number of scientific facts without occupying itself with the practical deductions which may be drawn from these. The effects of the rarest chemical upon the rarest form of fern are as important to it as is the action of digitalis in cardiac disease. But since we will not study it as an abstract science, but as a part of medicine, we shall lay stress principally upon its practical application. It is none the less impossible to give a good knowledge of the subject, even from a practical standpoint, without taking up some substances which are not of present importance, either as medicines or as poisons, for the list of these is constantly changing. Just as every physician has his own materia medica, so has every country, every generation, every year.

It must also be remembered that this book is intended for study as much as for reference, and, consequently, such effects as are obtained from a large number of drugs are studied more particularly on those drugs in which the action is most characteristic, even if these drugs should not be so widely known.

The **objects of pharmacology** are: (1) To determine the chemic structure of medicines; (2) the functional changes which they occasion; (3) their fate in the body.

The Relations of Pharmacology.—From the above definition it will be readily seen how closely pharmacology is connected with other sciences. Firstly, in its *methods*, which are only modifications of those employed in other research. For its intelligent study it requires as a preliminary a knowledge of the anatomy, histology, chemistry, and physiology of the living body, normal and as modified by disease, as well as of the chemic structure of the modifying substances (medicines).

It is related in particular to *chemistry*, in that it deals with chemic substances; in that the composition of these often gives valuable clues to their actions; and, further, in that all pharmacologic actions rest on a chemic basis; they are, in fact, reactions between the reagent and the living protoplasm.

It is related to *physiology*, and through it to *histology* and *anatomy*, in that it studies the modifications produced in physiologic processes and structures by pharmacologic reagents.

It is related to *pathology* and *clinical medicine*, since its utilitarian aim is to reduce pathologic processes to the physiologic. Unless the former are well understood, it is, of course, impossible to apply a rational remedy.

On the other hand, pharmacology, treated simply as a biologic science, has given valuable aid to all of these branches. It has aided medicine, in that it alone made rational therapeutics a possibility; pathology, in throwing light upon pathologic processes, such as, for instance, the infectious diseases. It is a frequent aid in physiologic investigation, poisons serving to stimulate or paralyze structures inaccessible to the scalpel or electrodes. It has also been used in histology: The action of atropin is one of the most ready methods of differentiating between striped and unstriped muscles. In chemistry pharmacologic action has even been used to aid in the determination of doubtful constitutional formulas.

It has in recent years been shown that many processes of the normal and pathologic organism are dependent upon what are strictly pharmacologic actions. We need only mention animal extracts, toxins, antitoxins, coma diabeticum, etc.; and the end of this has not yet been reached.

It is, of course, impossible to avoid a certain amount of overlapping of these sciences, but in view of the importance of the subjects, it will be no disadvantage to have them presented from several points of view.

3. Nature of Pharmacologic Action.—Pharmacologic action must be conceived as purely chemic. The action of the substance produces often the same changes in the living as in the dead organism; *e. g.*, H_2SO_4 and other caustics. Other substances produce changes mainly or solely in the labile living molecule; *e. g.*, many of the extremely active muscle and nerve poisons, as most alkaloids and glucosids.

While we cannot as yet attempt to explain all the phenomena of life by physical and chemic laws, we know, nevertheless, that a certain chemic integrity is necessary for the proper performance of their functions. When we change this in any way, when we introduce into the protoplasm a strange molecule, things go entirely different. We must remember that the chemic combination of the molecules of protoplasm is not so much of the nature of the combination of Na and Cl, but more of that of NaCl with H_2O in a solution; and when we speak of their changing in chemic composition, we often do not mean such atomic changes as those occasioned by the carbonizing action of H_2SO_4, but rather as those of precipitation of globulin by water.

It is indeed impossible, with our present knowledge even of dead proteids, to set up equations for such actions. When the enormous complexity of these molecules is borne in mind, it need not surprise us to find that we cannot always oversee their actions. Pflüger illustrates the relative size of the living protoplasmic molecule to that of the ordinary chemic molecule by comparing it to the difference in size of the sun and of the smallest meteor. The number of atoms entering into such a molecule must be high in the thousands. Living organisms are, therefore, very far from being as simple in their reactions as test-tube reagents. It is at present quite impossible to say, from any chemic standpoint, why strychnin should attack the central nervous system rather than the peripheral nerves, nor is it always true that drugs of similar composition have the same action, as we might argue from this theory of chemic action. None the less the rule is so frequent, that substances of similar structure do have a similar action, and similar structures are affected by the same drug, that it supports the chemic theory. There are, indeed, very many factors here which we do not understand; but we are in possession of some facts which help to throw light on the subject. Thus, drugs having the same elementary composition do not always have the same constitution; *i. e.*, they are isomeric. Isomeric compounds differ among themselves, not only in their chemic, but also in their physiologic, action. Thus, for instance, the compounds of carbons and nitrogen with organic radicals: In one class of these the nitrogen is trivalent, in the other quinquevalent, giving respectively:

$N^{III} = R—C \equiv N$: Nitriles, comparatively inactive.

$N^{V} = R—N \equiv C$: Iso-nitriles, very poisonous.

In homologous series the action of the drugs is found to change in a regular manner, just as other functions; for instance, with polyatomic alcohols, the permeability of red corpuscles varies inversely as the number of OH groups. So that the chemic constitution will, at times, enable us to explain an action or to forêtell the probable effects.

In a few cases we are beginning to see the reasons for the action; *e. g.*, in the case of penetration we find a parallel behavior with non-living substances. Again, the action of alcohol can be explained on a physical basis (solution of the fatty constituents of the cell). The cathartic action of neutral salts is due to their drawing water into the intestines by purely physical processes. Many poisons, especially HCN, produce changes in every way like those of asphyxia. They act, therefore, by interfering with the power of assimilating oxygen.

On the other hand, the various tissues react differently to different drugs, even with regard to such a comparatively simple process as penetration. Ferrocyanid, ferricyanid, and oxalate of ammonia, *e. g.*, penetrate red blood-corpuscles quite readily, whereas they are not absorbed from the intestine. Sulphates are not absorbed from the intestine, but they pass with great ease through the kidneys. Per contra, alkaline chlorids are readily absorbed from the intestine, but do not penetrate the corpuscles.

It is apparent that the chemic constitution plays a great part. While this cannot be carried out in detail, still in a great many cases the chemic constitution determines the pharmacologic actions. Examples of this will be mentioned in connection with the different groups (hydrocarbons, narcotics, nitriles, etc.).

On the other hand, identical actions may be obtained from substances having a totally different chemic character. Such resemblances are seen in cholera and arsenic, strychnin and tetanus, barium and digitalis, apomorphin and copper; and instances of this kind might be multiplied almost indefinitely.

The effect of drugs upon the tissues consists entirely in heightening or lowering their normal functions. The former is called *stimulation;* the latter, *depression.* (Irritation is a term used for stimulation accompanied by inflammatory change.) No new function can be created by any substance.

It results, from this, that the possible effects of the drug are comparatively limited. The complicated picture which we sometimes see is due to the number of different systems affected. Upon the whole, the phenomena are those of death. In dying tissue, also, we have first an increase and then a diminution, and finally an abolition, of their normal function. In fact, many drugs—*e. g.*, HCN, atropin, and toxic gases—produce phenomena exactly resembling those produced by heat or asphyxia. As a rule, in the action of drugs we also have first a stimulation and then a depression, but there are exceptions to this rule. The stimulation may not be followed by a marked depression, or the latter may not be preceded by any stimulation, or, again, the depression may precede the stimulation; but these are exceptions.

The symptoms are, of course, most simple and most readily analyzed in tissues in which a single function predominates. The subject is, however, quite complex in such tissues as muscles and nerves in which any one of a number of functions—excitability, conductivity, etc.—may be modified; and, indeed, much work remains still to be done along this line. It is also complicated by the fact that a given phenomenon may be the result of any one of a number of causes. Thus, stoppage of the heart may result from stimulation or paralysis of a dozen different mechanisms. Here it is necessary to have recourse to the ordinary physiologic methods.

4. Methods of Pharmacologic Research.—As in the study of the complex phenomena of life we can arrive at an understanding of the rôle of each part only by isolating it as completely as possible, so we must do in pharmacology.

In a pharmacologic research we must study, first, the reactions of the pharmacologic reagent with the isolated chemic constituents of the body (proteids, ferments, etc.). We must then study their action on lower organisms—*e. g.*, bacteria, amebæ, other protozoa, etc.; next, on isolated living structures, such as muscle and nerve, and isolated organs. We must then produce artificial alterations by various physiologic conditions, such as the division of the vagi in studying the action upon the heart muscle. Where a structure is inaccessible, we must often be content with experimenting upon analogous structures; *e. g.*, the effect of drugs upon the smooth muscles of the eye is often deduced from its action on the smooth muscle of the stomach. This is, of course, an indication rather than a proof.

In experimenting upon the whole animal, it is extremely important to observe all the phenomena, since only in this way is it possible to assign the proper place to each. The symptoms of drugs are especially apt to be variable when they affect different areas; thus, if they have both peripheral and central action, or if they affect a part of the central nervous system where a number of centers are situated; in the latter case the stimulation is apt to spread.

In experimenting with a new substance, the method should always be to advance from the lower to the higher, from the more simple to the more complex, organisms. From the protozoa we should advance to the frog and other cold-blooded animals; then birds, herbivora, carnivora, omnivora, the experimenter himself, and other healthy individuals; and not until this series has been completed should we try the drug on patients. In certain cases it may, of course, be quite proper to omit many of these stages, but the practice of trying new drugs at once on patients cannot be too much discouraged. In every case the physician, to gather reliable therapeutic information, must go about the employment of medicines as the scientist goes about an experiment. He must make the conditions the simplest, the observations the most exact possible.

5. Local and Remote Action.—The difference which we have noticed in the penetrability of blood-corpuscles, etc., allows us to understand that drugs have a selective action on certain tissues.

Caustic poisons, with violent chemic action, act almost equally on all the tissues. They may, therefore, have a *local action*. Some poisons do not act when applied to the skin, since they do not destroy it and cannot penetrate it, but if brought into direct contact they will kill any tissue. These are called *protoplasmic poisons.*

A very large class of poisons, however,—namely, those which have a molecular action,—affect most strongly, or even exclusively, certain particular structures (*muscle-nerve poisons*).

This selective action depends, probably, on chemic or functional differences in those tissues; *e. g.*, the drugs of the alcohol group, acting, as they do, by dissolving the fatty portions of the cells, will act most strongly upon those cells in which fat has a large functional importance.

The different action of drugs makes it necessary to distinguish several classes of symptoms, and it is well to have the terms employed for these defined as sharply as possible.

We speak of a *remote action* when the symptoms arise from structures not situated at the point of application; *local action*, when the symptoms are produced at the point of application. *General action* denotes the effect produced on the body at large directly or indirectly. *Systemic action* is the effect produced by the drug after its absorption. *Immediate effects* are those which occur at once. *Late effects* are those which occur after a time. *Direct effects* are those changes of functions which the drug produces directly. *Indirect effects* include the symptoms which arise, not as the direct effect of the drug, but as a secondary result of the direct effect;

e. g., if the drug paralyzes the heart, this would be a direct effect. If the blood pressure falls as a consequence of this cardiac paralysis, this would be an indirect effect.

6. Value of Pharmacology.—This different susceptibility of the tissues underlies, to a great extent, the difference in the susceptibility of different genera, species, and individuals. Although similarity of action of the same substance on different animals is the rule, exceptions are sufficiently frequent to justify the question often asked, namely, "*To what extent can we transfer the results of animal experiments to man?*" The answer is much the same as in Physiology.

The properties of protoplasm are identical whether we find them in the lowly ameba or in the highly specialized cells of the dog or of man. Similarly, the same organ has almost identical functions in related classes of animals. The dog's skeletal muscles do not differ essentially from the human in their physiologic actions.

In general, and we know of no exception to this rule, *the same physiology means the same pharmacology.* Physiologic differences will, however, produce changes in the pharmacologic effects.

An enumeration of some of these differences may be interesting: The rodents are incapable of vomiting, and are, therefore, immune to *emetics*. *Atropin* produces a quickening of the heart in dogs, but scarcely any in rabbits, for in these animals the vagus is not active. Atropin does not dilate the bird's pupil, whereas it dilates the pupil of nearly all other animals. This is accounted for by the fact that the bird's iris is composed of striped muscle. A snail will stand a dose of *strychnin* which would kill a man, the reason being that strychnin kills by its effect on the central nervous system, and, therefore, its most pronounced action is on those animals whose central nervous system is most highly developed. Similarly with *morphin*. A rabbit would not be killed by an amount of morphin which would be fatal to a man fifty times its weight, etc. Chickens are almost immune to oxalates if given by the mouth, because they are rendered insoluble by the calcium present in the alimentary canal of these birds.

There are, however, a number of differences which we can not so easily analyze; *e. g.*, frogs are very sensitive to drugs of the *digitalis* group, while toads are scarcely affected. (But this may be related to habituation, since the skin of the toad secretes normally a digitalis poison.) One species of frog, Rana esculenta, is thrown into tetanus by *caffein*, while Rana temporaria is thrown into rigor. *Potassium chlorate* causes the formation of methemoglobin in a number of animals, but not in the rabbit. Rabbits, goats, guineas, and rats are very resistant to *atropin*. The hedgehog is immune to snake venom and also very resistant against other poisons. So, also, rats are very much more resistant than guinea-pigs. The different susceptibility of various animals to bacteria and their poisons is well known.

The answer to our question: "In how far is one justified in transferring to man results obtained on animals?" depends upon their physiologic relation. While the latter even is not always too well known, still experience has taught us where it is safe to draw conclusions, but it enjoins upon us to be cautious in the interpretation and generalization of our results.

The failure to bear in mind the difference in physiology of different animals explains very often the apparently contradictory data obtained in experiments by those using different animals.

It is well to bear in mind that the greater difference between man and the lower animals consists in the greater development of the central nervous system, and especially in the psychic areas. The results obtained from animals are here of very little value.

The value of pharmacology lies in pointing out the mode of action of substances, especially in toxic doses.

Valuable as this indication is, it must be regarded as the first step only in the employment of the substance in disease. Its therapeutic value, its manner of action, and the exact indication for its use, must be determined by actual trial according to the ordinary methods of clinical investigation. Among these the statistical method, which is of comparatively recent introduction into medicine, holds first place. But necessary as is this clinical test, it is impossible, for want of material, to use it upon all new remedies which are constantly being introduced. We have but to cast a glance upon the numerous compounds which have been offered in recent years as curatives of tuberculosis, or for the reduction of fever, to become convinced that it would be absolutely impossible to subject them all to thorough clinical tests. It is here that pharmacology must step in and decide which of these drugs will repay further investigation. Without it, the physician would be obliged to grope in the dark. But its usefulness is at least as great with the older and better known remedies. It is not so long ago since these were employed on a purely empiric basis. In using them, the physician was guided by purely superficial resemblances, or at most by purely speculative hypotheses; but it is only when he thoroughly understands the action of the substance which he employs, as well as the condition existing in the patient, that he can foretell the result with any degree of safety. The somewhat bitter feeling which existed at one time between the clinician and pharmacologist, and which now has happily disappeared, was due to the misunderstanding of the rôles of the two branches. The objections urged against clinical data by the pharmacologist are the same as those urged by one clinician against the other. The ground which the experimental pharmacologist is justified in taking is, that incidental observation is not as conclusive as experimentation in which the conditions can be adjusted to suit the experimenter; that the amount of clinical evidence necessary for conviction is greater when it goes against, than when it agrees with, experiments; that the only clinical method which demonstrates facts is the statistical. The error of drawing conclusions from the hasty observations of a few cases has been only too well illustrated in the host of new remedies which have for a short time enjoyed popular favor, only to be discarded. And the fact that even very wide observations, when not joined with rigorous scientific methods, are apt to lead to false conclusions, is shown in the rise and fall of venesection.

On the other hand, the pharmacologist must be cautious in drawing inferences from negative results; for with these he only proves that he has not obtained the claimed results, which throws doubt upon them, but does not disprove them. He is, of course, absolutely wrong when he insists that results obtained upon a dog *must* be applied to man.

7. Individual Susceptibility and Immunity; Habituation and Cumulative Action.—The differences in different genera and species, although we cannot in all cases explain them in detail, will hardly surprise us, but there are also differences in individuals of the same species which appear more mysterious. These probably depend upon various causes, only some of which are known to us, and the importance of which we are just beginning to appreciate.

In a large series of experiments with toxic doses of drugs on animals the author has found that there is a fair degree of uniformity in the proportion of animals which died with a given dose. Thus, certain limits can be found inside of which, out of five animals three will always die. These limits vary from 0.5% (strychnin) to 25% (ergot), but are usually comprised within from 5% to 10%.

On the other hand, the susceptibility of any one animal is subject to greater possible variations; *e. g.*, with a given preparation of digitalis. 0.6 mg. per gram will always kill three guinea-pigs out of five. But in a large series of experiments, a number of animals will be found which will die of doses as small as 0.4 mg , while others will die only when 0.9 mg. is reached. Whether these comparatively immune animals always enjoy this immunity, or whether the condition is only temporary, as well as the influence of age, sex, etc., has not been determined.

These individual differences are still more striking if, instead of observing the toxic doses,—*i. e.*, the sum total of the effects,—we direct our attention upon some one particular action, *e. g.*, the amount of slowing of the heart or the variation of blood pressure. The differences in this respect are so great qualitatively that it is undoubtedly unsafe to draw conclusions from a single experiment, and it is absolutely impossible in these cases to establish any quantitative standard.

Such idiosyncrasies have been very often observed in man with almost all drugs which are commonly used. They consist of extraordinary susceptibility or tolerance or entirely atypical actions. The latter are a subject about which almost nothing is known. As to conditions influencing the former, we have now considerable information, although perhaps even more is still obscure.

Factors Influencing the Susceptibility.—Of the greatest importance among these is the fate of the poisons in the body. Poisons acting very violently or for a long time may produce such profound changes in the cells that the latter will never resume their normal function, and either die outright or continue in a pathologic condition.

In a few cases (digitalis, tetanus, etc.) the action may continue after the removal of the poison. It is not known whether the poison is in this case fixed in the cells, or whether we are dealing only with a persistence of the change.

For the most part, however, cells recover their normal function, and the deleterious influence of the poison disappears with the poison itself. Were it not for this fact, the administration of all drugs would be impossible. The disappearance of the poison is effected either by elimination through any excreting channel of the body, as with all inorganic poisons; or through its destruction in the body with formation of harmless decomposition products. The quickness of the former will depend upon the efficiency of the excreting organs; the latter—destruction—depends upon the activity of the particular kind of metabolism effecting this change.

Arsenic, *e. g.*, is far less poisonous in subcutaneous injections than when injected directly into the blood, because it combines with tissue elements, and, therefore, is much more slowly absorbed. Strychnin is also partly oxidized in the body, as has already been stated. The strychnin symptoms are very much lessened if the animal is placed in an atmosphere of oxygen, and this it shares with certain other tetanizing poisons. It is also stated that if the fatal dose is injected into the leg of the animal, but prevented from reaching the circulation of the animal for an hour, it has absolutely no effect.

Again, the action of many poisons is destroyed when the poison is taken by the stomach, because the activity is destroyed by the gastric juice, or by ferments in general. Here belong particularly the various toxins. Another organ which is especially active in the destruction of poisons is the liver. It owes its effects perhaps partly to the formation of insoluble compounds with bile acids. Poisons which are especially weakened by passing through the liver (*i. e.*, which have much stronger effects if injected through the jugular vein than through the mesenteric) are: curara, strychnin, veratrin, quinin, atropin, hyoscyamin, and morphin. Not all poisons are affected in this way; *e. g.*, arsenic. It may be remarked that this work upon the protective function of the liver is old, and is much in need of repetition and revision.

Caffein is more toxic in animals destitute of thyroids. This, perhaps, may be accounted for in the lowering of the oxidizing process produced in this manner. It would be extremely interesting to extend these observations to other drugs, particularly strychnin, and to animals in which the oxidizing powers are lowered by other processes, particularly castration. Low susceptibility by destruction of poisons is also very beautifully illustrated in the case of morphin: in acute morphin-poisoning something like 60% of the poison is excreted unchanged; whereas, in chronic morphin-poisoning, very much larger doses disappear completely. As another instance of the importance of the change in the body may be mentioned hydrocyanic acid. With HCN, subtoxic doses, repeated at intervals longer than necessary to destroy all the poison, will eventually kill the animal. We are evidently dealing with the exhaustion of the destroying mechanism.

In addition to the destruction of the poison, there may be a chemic neutralization, with the formation of innocuous compounds; such, *e. g.*, is the action of antitoxins.

Carbolic acid is bound in this manner by sulphates. Systemic poisoning by acids is prevented in most animals by their combination with the alkalies of the body.

Absorption.—The effect of a drug upon animals will depend very largely upon the relation of its disappearance to its *absorption*. The latter is again determined by a number of factors.

The Nature of the Drug.—Volatile poisons, as a rule, are absorbed very readily. HCN will produce its symptoms in a few seconds; whereas certain metals—*e. g.*, lead—will take many months to show their characteristic action.

A striking instance of the importance of absorption upon the effects of drugs is furnished by arsenic and antimony. Clinically, poisoning by these presents an entirely different picture and has very little in common. When injected into the circulation, however, they show very similar actions. The difference is due to the fact that arsenic is absorbed very readily and antimony with great difficulty.

Conditions in which there is a change in the solubility of the substance are, of course, very important factors. The presence of food, and especially of inert, non-absorbable matter, such as gums, will greatly retard the absorption of poisons. This is the reason why galenic preparations (tinctures and extracts) sometimes show different effects from the alkaloids to which they owe their activity.

It is for this reason also that pills especially are so slow in their action. The presence of inert matter (extractive) also retards the absorption on subcutaneous administration.

Place of Introduction.—The quickest and most violent effects are observed on *intravenous injection.* Here also the effects may appear quite different from those observed after administration by the stomach or skin, for when injected into a vein, a drug will reach the heart in a much more concentrated form than would otherwise be the case. With *subcutaneous injection* most drugs are absorbed fairly rapidly. Strychnin, *e. g.*, will produce its effects within two or three minutes. In the case of soluble substances, absorption is seldom delayed longer than ten to fifteen minutes. When the drug is administered by the *stomach*, the absorption will be influenced, first, by the amount of food and liquids in the stomach. This may act, not only by the presence of a large amount of inert matter, but also by entering into chemic combination with substances introduced. This is the case especially with articles of food containing tannin (tea, cranberries). The acidity of the stomach, the state of its functional activity, and the circulatory conditions will all have an influence upon the rate of absorption, so that this is quite variable.

Absorption is still slower and less complete when the drug is given *per rectum.* The *relative doses* by subcutaneous, oral, and rectal administration are as 1 : 2 : 4.

Drugs may also be introduced into the system through the lungs by *inhalation*, as in the case of anesthetics. Finally, they may be introduced through the skin (mercurial ointment). For the latter purpose it is necessary to have them in an oily solution. Watery solutions are not absorbed by the skin, except the active ingredient be volatile.

The reason for this non-absorption lies in the fact that the stratum corneum of the epidermis is absolutely non-permeable to solutions. Absorption must take place through the glandular structures of the skin, and these are filled with fatty matter, which prevents the penetration of watery solutions, but not, of course, of other fats.

It must be borne in mind that the application of solutions to open wounds or abraded surfaces is practically the same as subcutaneous injection, and absorption occurs in this case very readily.

After a drug is absorbed, its action is influenced by the *rapidity with which it penetrates from the blood into the tissues*, for, with the exception of a few poisons which change the blood itself, it is on the organs that their main action is exerted.

The time during which drugs remain in the blood is a subject well worthy of more investigation. We now have only a few data of this character:

Cyanic compounds disappear in 2 to 6 minutes.
Arsenic compounds disappear in $\frac{8}{10}$ to 30 seconds.
Tetanin disappears in 20 seconds.
Venin disappears in 10 minutes.
Diphtheria toxin disappears in 4 minutes.
Antitoxin disappears in several hours.

These data refer to just toxic doses administered by intravenous injection. If larger doses are given, they will, of course, require a longer time for their disappearance.

It will be seen from this table that, as far as is at present known, poisons as dissimilar as HCN, As, and toxins all disappear from the body extremely rapidly—inside of six minutes under the given conditions.

These facts throw doubt upon the theory which has been advanced to explain the beneficial effect of salt-solution injection in toxic conditions; namely, that by the injection of salt solutions these poisons will be "washed out" of the blood. As we see, they really do not exist in the blood, but in the tissues. It is, of course, not impossible to conceive that the poisons may also be washed out of the tissues by this method, but this has not yet been sufficiently tested. It is probable that the beneficial effects are due to the stimulating action which the injection of salt solution has even on the normal animal. A large proportion of the poison probably goes from the blood into the lymph, but about this we possess still less information.

Tolerance may exist through: Greater power of excretion than absorption (curara); greater destructive power (morphin); greater neutralizing power (acids in carnivora; toxins); greater resisting power of the organism: adults, as a rule, are more tolerant even by weight than young animals. Any condition which lowers the general "resistance" of an animal in any way, lowers it also against poisons; *e. g.*, guineas may be made more susceptible to atropin by lowering the alkalinity of their tissues.

Tolerance may also exist through *habituation.* Besides the greater destructive power, as in morphin, or the development of antitoxin substances, as in bacterial poisons, there is also a true functional habituation; that is to say, an animal may acquire the ability to tolerate poisons without in any way destroying or neutralizing them. The habituation to alcohol and nicotin, and perhaps also to arsenic, are instances of this.

It is an interesting fact that functional habituation, when acquired for a particular drug, holds also for other drugs having a similar action. A habitual drunkard, *e.g.*, is affected very little by anesthetics. Whether this extended immunity also holds true of other allied drugs, such as morphin and cannabis indica, has not been determined.

When the tolerance of an animal to a poison is *congenital*, it is more frequently called *immunity*. Such an immunity may be absolute or relative, probably always the latter.

Instances of this are the insusceptibility of the hedgehog to many poisons, of the rat to digitalis, of rodents to emetics, of herbivora to the atropin series, etc. It is, of course, most strikingly illustrated in the case of bacterial toxins. For these, the immunity resides in the serum, and is due to the presence of a peculiar property connected in some way with the proteids of the serum (globulin). Serum is also protective against some other poisons: the hemolytic properties of solanin and some other poisons are abolished by it.

The opposite of habituation is *cumulative action; i. e.*, an acquired susceptibility by which a given dose will produce greater effects than it did originally. This may be brought about in several ways: by greater capacity for absorption than excretion (lead); by inconstant absorption, where successive doses of the drug may lie unabsorbed in the alimentary canal, to be finally taken into the system *in toto* when the conditions are favorable to absorption. This is frequently the cause of the cumulative action of digitalis, and it explains the fact that the greatest individual variability to toxic doses exists precisely for those drugs which are absorbed with the greatest difficulty.

Cumulative action may also arise through *summation of effects*. The effect of the preceding dose may not have disappeared when the succeeding dose is given. The system appears also to be subject to what might be called an "education" to the effects of the drug. This is seen particularly in drugs acting upon the central nervous system. It is found, *e.g.*, that the susceptibility to strychnin increases with its administration, and it would seem that this is caused by the central nervous system becoming educated to the stimulating actions and responding to them more readily.

Another cause of cumulative action is the lowering of the resisting power produced by the preceding doses, or by using up the products required for the neutralization of the poison.

There are still *other conditions* which influence the effect of the poisons. The *weight* of the animal: the dose, as a rule, is usually very nearly proportional to the weight (minus the adipose tissue). The *age* of the animal: as has been stated, young animals are more susceptible than older animals.

There are drugs which show particularly marked differences according to the age. Children are especially susceptible to morphin, comparatively insusceptible to strychnin. Very old people are generally less resistant than adults. They bear purgatives and emetics especially badly, and, further, it is always necessary to bear in mind the existence of atheroma in giving drugs which raise the blood pressure.

Sex: This has not been investigated very thoroughly in animals. Women usually require smaller doses than men, but it has not really been made out whether the difference can be accounted for by weight or whether there is greater susceptibility. In pregnant women, drugs which cause hyperemia of the abdominal organs—*e. g.*, cathartics—will tend to produce abortion. The *time of day and surrounding conditions:* Soporifics will act much more promptly when given so that the action will fall at the normal sleeping time. The action of diaphoretics and diuretics may be modified by external heat or by the amount of liquid taken. The *presence of other drugs in the body:* The effect of a drug will, of course, be greater when another similarly acting drug is present in the body. Furthermore, great stress was formerly laid on what are called the synergistic properties of drugs. Drugs are called *synergistic* if, when taken together, they produce greater effects than if either were taken alone even in corresponding doses. This effect, the existence of which cannot be doubted, has not received sufficient attention at the hands of experimenters.

It is probably to be explained by the theory that certain useful actions are summed up, whereas undesirable actions are neutralized.

Drugs, on the other hand, which oppose each other in their action are spoken of as *antagonists*, their simultaneous administration constituting therapeutic incompatibility.

Here also only certain of the actions are opposed, whereas others are summed. For instance, whilst certain doses of atropin lessen the fatality of morphin, doses but very slightly larger prove much more fatal than either morphin or atropin alone.

Pathologic conditions: These have a very large influence upon the action of drugs.

This may be because the normal structures are modified, *e. g.*, digitalis, which acts upon the cardiac muscles, will have very much less effect if the cardiac muscle has been replaced by fatty tissue. Again, the diseased processes may modify the absorbing power of the organism: *e. g.*, Drugs given by the stomach, in cholera, will have very little effect, because they pass through the stomach before they have time for absorption. Fever is another condition which affects the action of certain substances very profoundly. Antipyretics have very little action upon the normal temperature, whereas they depress fever temperatures even below normal. Again, diseased processes may develop what appear to be new functions, such as epilepsy, and drugs like bromids have then quite a different action. Similarly the uterus is differently affected by drugs when pregnant than it is otherwise.

Experimentally the action of drugs may be affected very much by *heat and cold.* We have a physiologic analogy for this in the different effects of stimulating the vagus in the frog, with and without the application of heat. As a rule, poisons have less effect at a lower temperature. The susceptibility to the action of tetanus toxin or strychnin is very much lessened if the animal is cooled. The same holds true of chloral and alcohol. Morphin and curare, on the other hand, are less fatal if the animal is kept warm.

8. Methods of Administration.—These must vary according as to whether a local or general action is desired.

Local Administration.—Drugs may be used locally either to protect a surface, or for reflex effect, or as antiseptics, or as stimulants. They may be applied to the skin in various vehicles : Firstly, in oils or salves. If it is desired to secure the absorption of the remedy or its deep penetration, vegetable or animal oil must be used, preferably adeps lanæ hydrosus (lanolin). Oleic acid presents the advantage that it holds certain substances in true solution (metallic oxids and alkaloids). Where the local effect alone is required, the mineral fats (petrolatum or vaselin) may be employed. The remedy may also be placed in aqueous solutions (washes), especially if intended for an antiseptic, or it can be used in powder form. Caustics may be used either as solids or liquids.

Local medication may be used also on other surfaces than the skin, if they are accessible ; *e. g.*, mucous membranes. They are usually used here as aqueous solutions (injections, washes, and gargles).

Local application to skin can be used for producing general effects, but it is only employed in those cases (mercury) where the stomach has to be avoided and subcutaneous administration is not possible. The principal objection to the administration of drugs by the surface of the skin lies in the fact of the uncertain absorption, an exact dosage being in consequence impossible.

Oral Administration.—This, the most ancient method, is still the standard one. Its advantage lies in its great convenience and in the absence of local irritation. Nevertheless, certain drugs do give rise to disturbances of digestion.

This can be avoided by giving them in such a form that they will not be dissolved in the stomach (pills), or by giving them at a time when the stomach is filled with food. Absorption is, of course, delayed in these cases.

Rectal Administration.—The stomach and small intestine may be avoided by giving the drugs per rectum, either in the form of enema or suppositories.

Enemata, when introduced for the absorption of the medicine, should be as small as possible, but not so strong as to produce local irritant effects. One or two ounces is usually the proper quantity. The dose per rectum is double that by the stomach. When enemata are employed for their mechanical effects, the amount must, of course, be much greater—one or two pints. These should be raised to the body-temperature.

Subcutaneous or Hypodermic Administration.—Although but recently introduced (by A. W. Wood, 1855), this method has rapidly become very popular. It has the advantage of being quicker and more certain in its effects, and the dosage is more exact than can be secured by any other method. The principal objection to it lies in the fact that while it is not very painful with some medicines, it is very much so with any irritating substance. There is also a tendency to abscess formation. This is frequently due to deficient asepsis, but certain substances (protoplasmic poisons) produce abscess formation even with the most rigorous asepsis. The hypodermic dose is about one-half of the oral dose.

Intravenous Administration.—This has been tried in recent years, but has not come into general use. While it is the quickest way of securing the action of the substance, the slight operation required is some objection. There is also considerable danger connected with it. Air may be introduced into the vein, and while the presence of a small bubble of air in the circulation of a man is not as dangerous as in that of a rabbit, it may lead to very serious results. Another factor which we have already mentioned is that the action of drugs injected intravenously may be quite different than when taken by other channels. They act upon the heart more directly and with less dilution. Many substances also have the property of clotting the blood, and unless the administration be very skilfully done, the result might be disastrous.

Inhalation.—This method is used only for gaseous medicines like anesthetics or oxygen.

When giving drugs by inhalation, it must be borne in mind that the effect does not depend upon the quantity given, but the concentration of the gas and the time during which it is administered.

Cataphoresis.—This process has been employed in dentistry to facilitate the penetration of cocain, but it has not as yet found very extensive adoption in medicine and surgery. It is a process by which the molecules are carried from the + to the — pole. The solution to be introduced must possess a higher conductivity than the liquid of the tissues.

Continuous and Daily Dose.—It is often desired to keep the patient more or less permanently under the influence of the drug. The manner in which this is to be done will depend upon the nature of the drug, and no general rules can be laid down. It is, of course, necessary that the original dose must have been completely absorbed and destroyed or excreted before it can be repeated. This is practically attained by giving the medicine "three times a day." But this is a periodic rather than a continuous medication. To secure the latter, a fraction of the original dose should be administered at more frequent intervals.

(B) HISTORY OF THERAPEUTICS.

If we cast a glance at the history of therapeutics, we are met with some very singular facts. Some of these will serve to explain errors which have long adhered and which still adhere to the subject.

We may imagine one of our remotest ancestors brought face to face with disease. How mysterious must have seemed to him the phenomenon that to-day he is strong, active, and full of life, and to-morrow, without any cause apparent to him, he is weak, listless, and about to die! What strong hold it must have taken upon his untutored imagination! How earnestly he must have sought for means to remedy it! Here he happened at once upon two apparently very different methods: a spiritual and a material. On the one hand, overpowered by the mysteriousness of the process, he lost himself in superstition. He deemed the disease due to malevolent spirits which could be appeased by prayers and incantations. This formed the principal materia medica of prehistoric ages, as it does of the modern savage.

On the other hand, chance and the observation of animals revealed to him that certain material products were also efficient. As long as he limited himself to actual observation, the results were usually good. However, he soon began to search for more of these remedial agents. In this search we must remember the total darkness which then existed regarding the nature of the action—both of the disease and remedy. In this darkness he was only too glad to be guided by any ray of light, without having the means to examine whether the light came from a beacon or was only an ignis fatuus. With the fantastic, half logical incongruity so characteristic of the untutored mind he assumed the most extraordinary relations.

It is interesting to observe a little closer the principles which guided the blind savage in his search for remedies. Having found that most active medicines had a bitter or disagreeable taste, he came to regard any such substance as beneficial. Thus arose a host of simples which are now stowed away to molder in the attic of science, and which might well be disregarded were it not that some zealot occasionally disturbs their well-earned repose and attempts to launch them as something new.

Nor did this love of the disgusting die out with the stone age. It was prolonged far into the middle ages. To it we can probably trace the employment of feces and urine, of smoked snake, and of others still worse.

At a later period of the middle ages it was tried to combine the spiritual and the material treatment. It was thought that the Deity alone could cure disease, but that He had given man material remedies, and in His wisdom He had put a seal upon them by which man might know them. Thus arose in due time what is called the doctrine of "signatures." According to this, the use of a remedy was suggested by a fanciful resemblance in shape or color to some organ; *e.g.*, the liverwort, the lungwort, bloodroot, etc. These are survivals of this custom. Even a name was sufficient. Silver was used in lunacy because it was dedicated to Luna.

On the other hand, alchemists had arisen with their pertinacious search for the philosopher's stone, which was to convert all metals into gold, and cure all diseases. In this search they gave their nostra extensive trial on sick and well. Antimony is related to have been so named by its discoverer because of its fatal effects upon his fellow-monks.

The school of spagirists was founded by Basilius Valentinus toward the end of the fourteenth century and reached its zenith of power with Paracelsus. They insisted upon the mystical virtues of Sb, As, and Ag, and chemicals in general, and stood opposed to the old Galenists, who used only organic drugs. Notwithstanding their mysticism, which flavors of quackery, we must thank them for the discovery of some of our most valuable medicines.

Thus, a mass of materials, rubbish and otherwise, was added to the various simples, etc. Having so well-stocked an armory, the physician of that day felt that he was not doing his duty unless he gave his patient the benefit of it all, and the "shot-gun" prescription flourished at its best.

A natural reaction against this set in, and had for one of its first results the establishment of homeopathy by Hahnemann, near the end of the eighteenth century. The Hahnemann system was by no means new. For the most part it had its roots much further back. It was the natural result of the then existing theory of "vitalism."

Hahnemann believed that disease depends upon a perversion of the purely spiritual vital powers and is entirely immaterial in its nature. Logically, a thing spiritual could not be combated by material remedies, and, hence, Hahnemann turned to a spiritual power which he believed to be bound up in plants and liberated by dilution. This liberation of the principles exactly turned their action around, so that the action of his dilutions was, he stated, exactly the opposite of that of the concentrated drug, and could be used for relief of such symptoms as the latter produced: *Similia similibus curantur*. This was the first tenet of Hahnemann. The second was that the nature of the disease being unseizable, it was not subject to treatment, but that only its symptoms can be treated. Hence, homeopathy, in so far as it follows the principles of its founder, has no place for the medical sciences, such as physiology, anatomy, pathology, or chemistry. Any one with an indexed book of symptoms and their remedies would be able to practice it without any elaborate study or preparation.

In marked contrast to the above is the third dictum: that the medicinal treatment must be supported by dietetic and hygienic measures.

Hahnemann's system was the natural outgrowth of his time. At present it is an anachronism, as his pupils are the first to acknowledge in practice, if not in words. But in his time Hahnemann accomplished considerable for medical science. He called attention to the importance of diet, etc., when this was only too much neglected; but perhaps the principal use of homeopathy has been to show to rational medicine the fact that disease tends to recovery without any medical interference.

This was, indeed, the next step which medicine took—total emancipation from all drugs. This dates from the establishment of the Vienna school by van Swieten, in 1745. The strongest advocate of nihilism was Skoda (1805–1881), the founder of the methods of percussion and auscultation. Such nihilism was absolutely necessary at that time, just as periods of skepticism are necessary in philosophy, and mark steps in progress. The accumulated refuse was so great as to bury the good. The only way was to empty out the whole and begin anew. This was a necessity then, but now nihilism is as obsolete as the gun-shot prescription. He who proclaims it, simply proclaims his own ignorance and want of critical faculty.

The reestablishment of therapeutics, founded now upon reason, was thus aided by the very man who had attempted to destroy it. For he established physical methods of diagnosis, and demonstrated the effects of disease as they had never been demonstrated before, making it possible also to demonstrate the effect of remedies.

Then followed the isolation of active principles (led by the discovery of morphin in 1817), thus substituting the definite for the indefinite drugs. Finally followed animal experimentation, by means of which modern pharmacology has developed.

Rational therapeutics is now on a firm basis. But, at the same time, the mystic has also been further developed, not only in homeopathy, but also in the many forms of suggestion. The value of suggestive therapeutics proper cannot be denied. It is a strictly scientific method of treatment, and is employed in its milder forms by every physician as "the personal influence" and the "faith in doctor and medicine." It often constitutes all there is of merit in those medical fads which have accompanied medical science since the oldest time.

One of the most important preliminaries to the rational treatment of disease is that the physician should understand that he cannot make a patient well. That is exclusively nature's task. "Nature" inevitably tends to bring the organism back to its normal condition, and the task of the physician consists in directing his treatment in such a manner as to remove obstacles from nature's path. Just as the surgeon cannot cause the union of a broken bone, but can only put it in the most favorable condition for nature to perform this union,—*i. e.*, set it,—so the physician cannot cure heart disease. He may either remove the condition which causes it, if still present, or remove by digitalis, etc., the factors which retard the cure; but in any case he must rely upon nature to perform the last, the really important act: viz., the permanent return to normal.

That nature not only puts the final touch upon every reparative process, but that she may take every step as well,—*i. e.*, that a patient may get well without any medical interference,—is too well known to require further discussion. The ways in which these processes of repair take place constitute one of the departments of pathology and medicine.

In the light of the above, it might well be asked: If nature is thus able to effect cures; if by far the greater number of diseases tend to spontaneous recovery, what is the function of the physician? Can he do anything but harm if he attempts to meddle with the great processes of nature? If he undertakes to aid, does he not really meddle? We must, in examining this question, lay the emphasis in the above sentence on "nature *tends* to effect a spontaneous cure." But nature is essentially blind in her workings. She works by general laws, which often do not take account of individual cases. Though we must recognize her processes as almost always the best under the given conditions, they may be greatly at fault quantitatively. Nature may do too much or too little. It is now conceded that fever, pain, inflammation, etc., are protective mechanisms; but when the fever becomes so high as to be in itself dangerous to life, when the pain is intolerable and constant, and persists after it is no longer needed, when inflammation spreads; then it is evident that the originally salutary process is becoming the reverse. That the processes of nature are often insufficient is evident from the fact that it does not in all cases effect a cure. Nature may sometimes be absolutely wrong; *e. g.*, in the desire for solid food in typhoid.

It is, then, the duty of the physician to judiciously modify the natural tendency, if he possesses the means of doing so. But he must do so wisely, or it were better not at all. He must understand the diseased condition; he must understand nature's way of meeting the difficulty; he must judge in what ways nature may be supported; and, finally, he must thoroughly understand the means at his command for the purpose—*i. e.*, pharmacology. As long as he is not clear in regard to these factors, he is merely groping in the dark, as likely at least to do harm as good. In this case expectant treatment is alone justifiable.

We see how from the above we can deduce a number of methods of treatment.

I. Expectant Treatment: i. e., the absence of any real attempt at treatment beyond hygiene, rest, diet, and other similar general measures; with the object of leaving the powers of nature free play. This should be employed in all cases where no better treatment is known; but, as has been said, it is usually within the province and power of the physician to support nature in her endeavor.

The expectant treatment must also be used when it is desired to let the disease progress to a certain point, if this is necessary for diagnosis. Thus, general treatment for primary syphilis is usually expectant, since no great benefit would result from immediate specific treatment, whereas the diagnosis would be greatly obscured thereby.

II. Symptomatic Treatment.—This is aimed at the symptoms of the disease without reference to their cause. This may be objectionable in some cases, indicated in others. In striking the symptoms one very often also strikes the disease. Again, the symptoms in themselves may be so objectionable or lead to such secondary results as to make their removal desirable. Pain, cough, and fever are all purely symptoms, and yet no one would refuse to treat them simply because unable to remove the root of the disorder. On the other hand, the symptoms may be very deceptive—a chill will not require external heat; a referred pain will not be relieved by local application of iodin to the place where it is felt.

In removing the symptoms the physician also deprives himself of the only index to the treatment of the underlying disorder. He must constantly be on his guard against believing himself successful when he has succeeded in removing one or several of the symptoms of the disease. In many cases the symptom may itself be salutary; in which case it would not do to remove it (*e. g.*, cough when there is hypersecretion of mucous; a certain amount of pain when rest is indicated in fracture).

It need scarcely be mentioned that it is not ethical to persuade a patient that he is being cured when he is in fact only being relieved of the symptoms.

III. Empirical Treatment.—This follows merely the dictates of experience without concerning itself about the reasons for these. While in the present state of our science it is still necessary to employ it only too often, it requires scarcely a thought to see how often it may be not only useless, but even injurious. Conditions which resemble each other very closely superficially may really be diametrically opposite, and may require very different treatment.

IV. Rational or Scientific Treatment.—While this makes use of the three preceding methods, it aims essentially at the removal of the cause of the disorder and to favorably influence its course. It presupposes a knowledge of both, as well as a thorough acquaintance with the manner in which they may be influenced by remedial measures.

While it relies, on the one hand, on the science of pathology, etc., for the revelation of the nature of the disease, it requires equally accurate knowledge of the nature of the action of drugs: viz., scientific pharmacology.

PART II.—SECTION A.

DRUGS WHOSE MAIN ACTION OCCURS AFTER ABSORPTION.

1. **Classification of Drugs.**—The classification of drugs can be done according to a number of principles.

By one system they may be classified, according to their origin, into chemic, vegetable, and animal drugs; the chemic again into inorganic and organic, and these according to the ordinary chemic groups; vegetable and animal, according to families. From our standpoint the objection to this classification is that the action of the different members of a family is quite different, or the same action is obtained from members of different families. Another method is the therapeutic. In this the drugs are classed according to their action; *e.g.*, we have drugs which slow the heart, drugs which quicken the heart, etc. The principal objection to this is that it is arbitrary. Many drugs possess several actions, and according to this system they have to be classed in several places, which makes a uniform idea of their action quite impossible. Again, by this method of classification the student receives the idea that all these actions are of equal importance, whereas this is often not the case. Lastly, it brings together drugs the action of which only bears a superficial resemblance. The slowing of the heart, *e. g.*, may be produced in many different ways. Another method is the clinical, which classifies drugs according to the organs on which they act or the diseases for which they are employed. This is open to the same objections as was the therapeutic method.

The system which we shall employ is Buchheim's,[1] which aims to unite similar drugs into groups on somewhat the same principle as is used in the natural classification of botany. Neither the chemic composition nor any other one characteristic is taken to determine the groups, but those having most characters in common are placed together, and one group runs into another.

One advantage of such a system is that one may begin its study at almost any point. We shall start with alkaloids, since these illustrate pharmacologic principles in the most striking manner.

2. **Muscle-nerve Poisons.**—In regard to their action alkaloids belong to a larger group which may be called muscle-nerve poisons. This group includes particularly all those poisons whose main actions are not local; in other words, all poisons which really enter the body and exert a general action affect mainly muscle and nerve tissue. When the great specialization of these tissues is borne in mind, the great complexity of their functions, their great susceptibility to disturbing influences, and, consequently, their great susceptibility to injury, this specialized action need not cause surprise. It must not be supposed that these poisons affect only muscles and nerves. In most cases they affect other cells as well, but it is in these specialized tissues that their effects are most conspicuous.

The selective action is not, however, to be explained merely by greater functional susceptibility, but is due very largely to a chemic affinity between the poison and the protoplasm—particularly the nucleus—of the respective cells. The protoplasm of the different classes of cells presents minute chemic differences which underlie this selective action.

The central nervous system, the peripheral nerves, the heart and vessels, glands, intestine, and skeletal muscles, all come under this heading of muscle and nerve.

Muscles and nerves are connected in a continuous chain, consisting, *e. g.*, of sensory end cell, afferent nerve, at least one ending and one cell in the central nervous system, efferent nerve, motor endings, and muscle cell. (See diagram, Fig. 45.) Theoretically, the poison may act on any one of these structures. As a matter of fact, it never acts on the nerve-trunk, except it be applied directly; the reason for this being that the endings and cells are much more sensitive than the fibers; of these, again, it appears that the endings are much more sensitive than the cells. Poisons act on these structures by increasing one or more of their normal functions.

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[1] Buccheim may be considered as the founder of modern pharmacology by the establishment of the first pharmacologic laboratory, at Dorpat in 1856.

Inasmuch as poisons typical of this group do not produce any local effect, they are characterized by the absence of postmortem changes.

3. **Alkaloids** (ptomains and leucomains).—*Alkaloids* are organic bodies, usually of vegetable origin, of a basic character uniting with acids after the manner of ammonia and giving well-defined and usually crystalline salts. Substances possessing all the properties of alkaloids, but formed by bacteria, are called *ptomains*. Somewhat similar substances, but not possessing all the alkaloid characters, are formed during the normal processes of the body,—*i. e.*, without the action of bacteria,—and are called *leucomains*. True alkaloids are formed by certain animals (in the skin of the salamander).

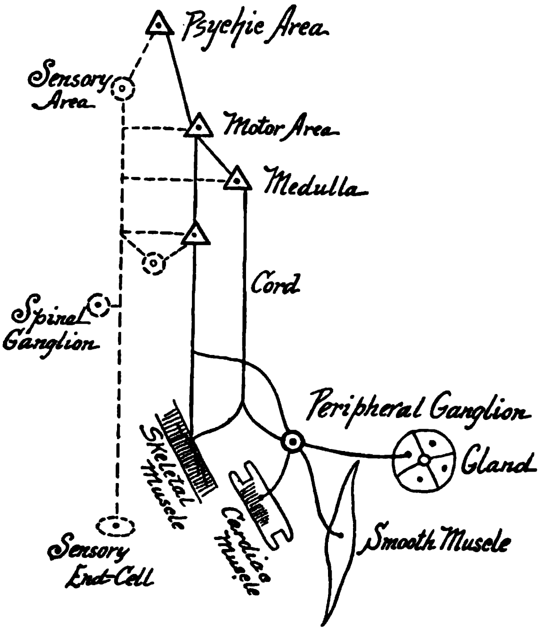


Fig. 45.—Diagram of the central nervous system, to illustrate possible points of attack of muscle-nerve poisons. The broken line indicates the afferent mechanism; the solid line, the efferent mechanism.

Alkaloids have been discovered only in this century. The following is a list of the *dates of the discovery of the principal alkaloids:*

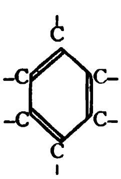
TABLE XI.

Morphin	1805–1817	Sertuerner.
Narcotin	1817	Robiquet.
Veratrin	1818	Meissner.
Strychnin	"	Pelletier and Caventou.
Piperin	1819	Oersted.
Delphinin	"	Lassaigne, etc.
Brucin	"	Pelletier and Caventou.
Quinin	1820	" "
Cinchonin	"	" "
Solanin	"	Desforses.
Caffein	"	Runge.
Chelidonin	1825	Godefroy.
Corydalin	1826	Wackenroder.
Berberidin	"	Pelletier and Pelleton.
Coniin	1827	
Nicotin	1829	
Atropin	1833	

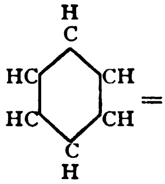
The Chemic Constitution of Alkaloids.—This is, for the most part, not fully understood, but many alkaloids are built up from a common nucleus, pyridin or quinolin.

It is interesting to note that albumin under the influence of concentrated HCl yields a small quantity of a pyridin base. The alkaloids of plants are also formed presumably by the decomposition of their proteids, and are supposed to form a partial protection against insects.

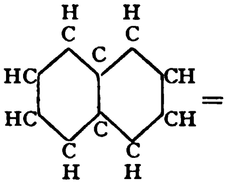
The following constitutional formulas will illustrate the structure of some of the simplest alkaloids:



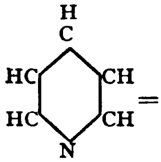
BENZOL RING.



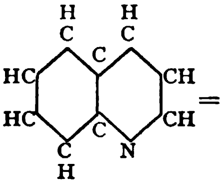
$= C_6H_6$ BENZOL.



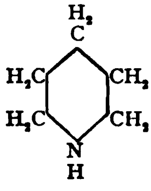
$= C_{10}H_8$ NAPHTHALIN.



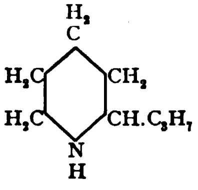
$= C_5H_5N$ PYRIDIN.



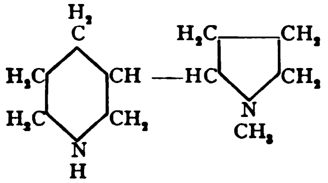
$= C_9H_7N$ QUINOLIN.



$= C_5H_{11}N$ PIPERIDIN.



= CONIIN.



= Nicotin.

The following table gives the *elementary composition* of the principal alkaloids (Dragendorff):

TABLE XII.

Aconitin	$C_{33}H_{43}NO_{12}$.
Atropin	$C_{17}H_{23}NO_3$.
Brucin	$C_{23}H_{26}N_2O_4$.
Quinin	$C_{20}H_{24}N_2O_2$.
Cinchonin	$C_{19}H_{22}N_2O$.
Cocain	$C_{16}H_{19}NO_8$.
Codein	$C_{18}H_{21}NO_3$.
Colchicin	$C_{17}H_{23}NO_6$.
Coniin	$C_8H_{15}N$.
Hyoscin	$C_{17}H_{23}NO_3$.
Hyoscyamin	$C_{17}H_{23}NO_3$.
Morphin	$C_{17}H_{19}NO_3$.
Narcotin	$C_{22}H_{23}NO_7$.
Nicotin	$C_{10}H_{14}N_2$.
Strychnin	$C_{21}H_{22}N_2O_2$.
Veratrin	$C_{52}H_{86}N_2O_{15}$.

It will be seen that certain of these alkaloids contain oxygen and others do not. Those containing oxygen are solid and comparatively non-volatile, whereas those free from oxygen (nicotin and coniin) are liquid and volatile.

All alkaloids have certain *properties in common:* They have a bitter taste, turn red litmus paper blue, have a very profound physiologic action, and leave no postmortem changes. They are soluble in ether, chloroform, and oils, much less soluble in alcohol, and comparatively insoluble in water. Alkaloidal salts, on the other hand, have just the opposite solubility: They are soluble in water and alcohol, insoluble in chloroform and ether. With the alkaloidal salts, the combined acid plays a prominent rôle in the solubility. As a rule, the chlorids are the most soluble.

Alkaloidal salts present the following *chemic reactions in common:*

1. **Nitrogen Reaction.** (See Chapter XXXIII.)
2. **Precipitates** are obtained with :

Hydrates and carbonates of alkalies and alkaline earths.

I + *KI*. All alkaloids; limits of sensibility 1 : 300 (best acidulated with H_2SO_4).

KI + *HgI₂* (Meyer's reagent). All alkaloids; limit of sensibility 1 : 1000 (best acidulated with HCl).

Phosphomolybdic acid. All alkaloids; limit of sensibility 1 : 300; very delicate (best acidulated with HNO_3).

Picric acid. Some alkaloids; limits of sensibility 1 : 500 (caffein).

$AuCl_3$. Most alkaloids; limits of sensibility 1 : 1000 (+ atropin, 0 codein).

$HgCl_2$. Limits of sensibility 1 : 500 (+ caffein, some time; 0 morphin).

$PtCl_4$. All alkaloids; limits of sensibility 1 : 2000.

$K_2Cr_2O_7$. Limits of sensibility 1 : 500 (+ strychnin, 0 caffein).

Tannin. Most alkaloids; limits of sensibility 1 : 300 (+ strychnin; 0, almost, morphin).

3. Color Reactions.—Alkaloids give characteristic colors with concentrated acids or similar reagents.

Examples:

H_2SO_4 concentrated: often colored liquids (veratrin).

H_2SO_4 + heat: morphin (first colorless) becomes red, violet, and green.

HNO_3 concentrated: morphin, orange becoming yellow.

4. General Treatment of Alkaloidal Poisoning.—This consists in neutralization and evacuation. These two are practically the same for all alkaloids. In addition to this general treatment, each alkaloid requires a special physiologic antidote.

Neutralization.—Any of the alkaloidal precipitants, if itself non-toxic, may be used for this purpose.

Tannin: Dose about ½ drachm (2 Gm.) or in the form of strong tea. The tannates of alkaloids are decomposed by acids, consequently by the gastric juice. It is, therefore, necessary to administer the tannin with alkalies (sodium carbonate or sodium bicarbonate). *Iodin + potassium iodid* (Lugol's solution) or *tincture of iodin:* This is given in doses of 15 drops freely diluted with water. The precipitate is redissolved by the alkaline juice of the intestines, hence they must be followed by a purgative. *Egg-white:* The weakest of these precipitants. It is used by mixing two or three whites of eggs in a quart of water and taking teacupful doses. *Potassium permanganate:* 20 to 50 grains (1 to 3 Gm.) in a pint of water. This will be efficient only if the stomach is comparatively empty.

Except the last, these precipitates are redissolved in some part of the alimentary canal. It is, therefore, necessary to follow them up by an emetic and a cathartic. If they are vomited spontaneously, this is rather an advantage, and it is only necessary to repeat the dose. It may be mentioned that any of these chemic antidotes may be added to the water used for washing the stomach.

Evacuation.—This may be effected either by the stomach-tube or by an emetic. The former may be used in all alkaloidal poisoning except strychnin. (In inorganic poisoning it cannot be used with corrosives.)

In the absence of a regular stomach-tube, a piece of rubber gas tubing will answer the purpose. The tube should not be forced down, but simply be pushed gently into the pharynx, where the pharyngeal muscles will effect its entrance into the stomach. If the patient struggles, it may be necessary to make use of a gag. When the stomach-tube is used, one should not only evacuate the contents of the stomach, but also wash out this organ thoroughly, preferably adding to the wash-water any of the chemic precipitants just mentioned.

Emetics.—Apomorphin: This can be given hypodermically in doses of about $\frac{1}{25}$ of a grain (2 mg.) in 1 % solution.

It possesses the advantage over the other emetics of much more prompt and certain action, and in the fact that it may be administered to a patient who would resist administration by the mouth. It has the disadvantage that it produces more depression than the metallic emetics.

All the following emetics are given by the mouth:

Zinc sulphate ($ZnSO_4$): 30 grains (half a teaspoonful) diluted in a tumbler of water.

Copper sulphate ($CuSO_4$): a piece the size of a pea dissolved in a tumbler of water.

Both of these act quite promptly with a minimum of depression.

Ipecac: ʒj (teaspoonful) of the powder or ℥ss of the wine.

This produces considerable depression.

Mustard: A teaspoonful stirred up in a tumblerful of warm water.

This is perhaps the most uncertain of these emetics, but it may be valuable in emergency.

The emetic must be repeated in fifteen to twenty minutes, if necessary.

Other measures consist especially in *artificial respiration.* This will be useful not only when respiration has absolutely stopped, but when it has shown the first signs of weakening.

Any of the ordinary methods of artificial respiration may be used. Caution, however, must be observed, for artificial respiration is not quite as devoid of noxious effects as is commonly supposed. Edema of the lungs, pleurisy, and even fracture of the ribs, are occasional sequels of violent artificial respiration. It might in many cases be replaced by inhalation of oxygen, when this is convenient.

Manual artificial respiration may be replaced by intermittent *faradization of the phrenic nerve*, but in this case there is always the danger of stimulating the vagus at the same time and of consequently slowing or stopping the heart, which is extremely undesirable when this organ is already depressed.

Another measure which is universally useful is the *application of external heat.*

In summing up these general measures, the principal matter to bear in mind is, that promptness is required above all things. When called to a case of poisoning, the physician should always have in mind before he reaches the patient what he has to do, because so often a few minutes' delay may be sufficient to turn the scale. The first thing to do is to administer any chemic antidote which is at hand, and, second, any emetic or the stomach-tube; third, the application of heat; fourth, if convulsions are present or the respiration is weak, artificial respiration; fifth, the appropriate physiologic antidote.

In studying the drugs, we shall, as far as possible, follow the subjoined plan:

Members of groups and their derivation.
Summary of actions.
Details of action.
Fate in the organism.
Relation to other groups.
Toxicology.
Fatal doses for animals.
Treatment of poisoning.
Therapeutic uses.
Materia medica.
Diseases treated especially by drugs of this group.

CHAPTER VIII.

CONVULSANT SERIES.

(A) STRYCHNIN GROUP.

I. MEMBERS.

Strychnin, Brucin, Thebain, Gelsemin, Calabarin, Tetanus Toxin.

Derivation. — The principal members of this group (strychnin, brucin) are derived from plants of the genus Strychnos, especially S. Ignatii and S. Nux Vomica.

These were unknown to the ancients, and are thought to have been introduced by the Arabs. The first good description occurred in 1540. Strychnin was discovered in 1818. The seed of nux vomica contains from 0.2% to 0.6% of strychnin, 0.5% to 1% of brucin. The bark contains the same principle in less amount, but relatively more brucin. It was formerly found in commerce under the name of "false angostura." Several arrow poisons are also derived from the genus Strychnos, especially the Upas Tieuté from Java. Some of the strychnos species do not contain any active principle.

Nux vomica also contains a small quantity of a third alkaloid, igasurin, which has not been very greatly studied, but which seems similar to strychnin.

II. SUMMARY OF ACTIONS.

1. *Heightening of the reflex irritability of the central nervous system from below upward, and finally paralysis of these structures.*
2. "*Bitter effect*" *upon the alimentary canal.*
3. In large doses it has a curare-like action upon muscle-nerve endings.
4. A paralysis of certain ganglia (the superior cervical sympathetic).

III. DETAILS OF ACTION.

(A) Central Nervous System.—1. Spinal Cord.—The principal symptom of strychnin-poisoning is an increased reflex irritability of the spinal cord, shown most conspicuously by the production of tetanus. The animal, frog or mammal, after a short period of increased reflex excitability is thrown into violent clonic spasms. (Spasms or convulsions are called clonic when they are intermittent, tonic when persistent.) There are sudden and violent contractions of all the muscles of the body, persisting for a few seconds or minutes; then there is complete relaxation, the animal showing all the signs of paralysis. After a few minutes the convulsions are repeated, to be again replaced by paralysis. With appropriate doses these phenomena may be repeated almost indefinitely (from eighteen to forty hours) with frogs, whereas mammals usually die after the first few convulsions.

Location of the Tetanus.—A tetanus or spasm may conceivably be located in the muscle, nerve endings, spinal cord, medulla, brain, or sensory endings.

The distinction between these different seats can be made most easily in the frog, but with the appropriate disposition can also be carried out in mammals.

Muscle and nerve endings may be excluded by section of the nerve-trunk. This stops the convulsions.

If the spasms in these structures had not ceased after section of the nerve, one could distinguish between them by the administration of curare. This would stop the contraction of the muscle if it had its origin in the stimulation of its endings, but not if it were located in the muscle-fibers. The character of convulsions would also give a clue. If situated in the muscle, the contractions would usually be tonic; if in the endings, fibrillar.

Brain and Medulla.—These can be excluded by successive section or destruction. If division below the brain or medulla stops the convulsion, the seat must be in one of the structures above the divided point.

The convulsions produced by stimulation of the brain or medulla have many characters in common. Both show a prodromal period, clonic and tonic spasms, and then coma (corresponding to the symptoms of epilepsy).

The symptoms produced by stimulation of the *cerebral center* in frogs have been studied recently by dusting the surface of the cerebrum with dry creatin, with the following results:

Four periods can be distinguished:

1. *Prodromal*, which begins at once; slight depression; respiration 15 to 20; animal recovers in five seconds to five minutes; respiration 30 to 90, strong reflexes, pupils dilated. Then excitement: the animal jumps, wipes nose and eyes. In five to ten minutes it jumps about as if pursued, and has paroxysms of loud cries; then movement becomes less coordinated: *e.g.*, it makes movements while in air.

2. Suddenly *clonic spasms;* the animal falls, with head bent in, the arms alternately stretch and bend, but gradually approach sternum, the legs are abducted and thrown forward and backward. This gradually passes into:

3. *Tonic spasm;* arms approach or cross over middle line; legs and back as in strychnin, head bent toward belly, abdominal muscles contract, long cry, respiration absent, heart very slow and weak; after a few seconds vibration of muscles, with occasionally stronger spasms. During the whole attack reflexes absolutely abolished.

4. After a time, the animal recovers partly and draws in extremities; it appears quite normal. In ten minutes there is another attack, beginning with the excitement. This may be repeated several times till death occurs.

The convulsions by stimulation of the *medulla* differ somewhat from those by cerebral stimulation, but have a great resemblance. They show the same succession of latent period, clonic and tonic spasms, and coma. The medullary center for convulsions in the frog is situated in the lower half of the fourth ventricle and is most conspicuous at a point near the calamus. Mechanical or chemic stimulation of this point causes the following symptoms: Cry, then a series of rapid and very characteristic movements. The animal throws his hind legs out and far forward to the side of his head; his arms are bent and touch near the median line; head bent down; through contraction of the muscles of the back, the animal turns backward somersaults; in these movements the legs become extended; he then turns on belly. Then the same movements are repeated five or six times. The animal appears thin through contraction of the abdominal muscles; trembling of the whole body; attack usually ends in coma; reflexes are much diminished, but not entirely abolished. Exactly similar effects follow chemic stimulants, as by creatin.

Cerebral stimulation, therefore, differs from the medullary, in the frog, in that it shows longer stages, acceleration of respiration, entire absence of reflexes, and no somersaults.

Stimulation of either the brain or the medulla also involves—*i. e.*, exhausts—the other center.

Section through the medulla does not destroy the spasms after strychnin. The spasms may, of course, be diminished for a short time by the shock, but the animal recovers and the convulsions resume, which would not be the case if their seat were above the cord.

The destruction of the spinal cord stops the convulsions entirely. This leaves the cord or the sensory endings as the seat of the convulsions.

These peripheral endings may be excluded by ligating a leg with the exception of the nerve and then injecting the poison. The leg will be seen to take part in the convulsions although its sensory endings are excluded from the poison. Or, still better, the lumbar cord may be isolated completely from the blood supply and then strychnin injected into the leg. By this method the leg does not show convulsions even though the sensory endings are exposed to the strychnin; whereas the spinal cord is not exposed. The convulsions show much more quickly and strongly if the strychnin is injected into the subdural canal. This fact also tends to support the opinion advanced.

It is evident, then, that the sensory endings are not the seat of the action.

Again, the convulsions might be conceived as arising through a *direct* stimulation of the centers (as in asphyxia); or through *reflex* stimulation (as in pain); or, finally, not from stimulation at all, but from the *more facile passage* of impulses.

The first, that is to say, the direct, stimulation of the centers is rendered improbable by the fact that in slight degrees of strychnin-poisoning the convulsions do not occur spontaneously, but only upon stimulation. In very large doses the stimulation required may, indeed, be so small as not to be perceptible and the tetanus may bear an automatic character. But that reflexes are involved here also is shown by the fact that the convulsions may be prevented by cutting off sensory impressions from the cord; *e. g.*, by placing a frog in a weak cocain solution, just strong enough to paralyze the sensory endings without producing central paralysis, or by dividing all the posterior roots.

That there is no reflex peripheral stimulation by strychnin itself is shown by the experiment mentioned: viz., ligation of the hind legs. Furthermore, direct application of strychnin to the spinal cord has the same result.

This leaves but one explanation: the more facile passage of the normal impulses. Strychnin tetanus must be conceived as caused by the extensive spreading of reflexes on the application of small stimuli (a spreading which is not normally seen except after the very strongest stimulation).

The resistance may be lowered at three different points; in the cells, the endings, or the nerve-fibers of the spinal cord. There is reason to suppose that the fibers of the central nervous system show relatively as little susceptibility to poisons as the peripheral fibers, and that the action is therefore limited to either cells or endings.

The exact location of the action of strychnin in the spinal cord has been the subject of extensive experimentation and speculation. Even at the present day no agreement has been reached. It seems impossible to resolve the problem definitely with the present physiologic methods, only the newer cytologic stains may lead to a more definite localization. It can be demonstrated that *the action is not situated in the posterior ganglia*, for stimulation of the roots central to these is effectual. Most recent experiments tend to show that the effect of strychnin consists in inducing a condition of greater excitability in both motor and sensory cells.

Filehne devised the following experiment to substantiate this theory. He isolated as completely as possible the lower half of the cord of a frog from its blood supply, and then injected appropriate doses of strychnin, in this way exposing the upper half of the cord to the poison, whilst the lower half remained unpoisoned. Stimulating the fore or hind limb, and observing the effects on the animal, he noted the following:

1. Stimulation of fore leg gives tetanus of the fore legs (reflex from poisoned sensory to poisoned motor).
2. Stimulation of fore leg gives short, but very prompt, contraction of hind legs (reflex from poisoned sensory to unpoisoned motor).
3. Stimulation of hind leg gives single short contraction of hind leg (reflex from unpoisoned sensory to unpoisoned motor).
4. Stimulation of hind leg gives tetanus of fore legs (reflex from unpoisoned sensory to poisoned motor).

2 shows that poisoning of the sensory cells alone causes a more prompt contraction; 4, that poisoning of the motor cells alone causes tetanus. *The seat of the tetanus is therefore in the motor cells, whereas the sensory cells are merely rendered capable of appreciating stimuli more sharply.*

This agrees well with what is known about the action of strychnin on the special senses: it effects here a greater acuteness, but no fusion of succeeding impressions, which would correspond to a tetanus. The reason for this apparent difference in the action of strychnin on sensory and motor cells lies, not in the strychnin, but in the proper functions of the nerve-cell. Strychnin places each in a state of greater excitability; but the sensory cell is constructed to express this by greater acuteness, the motor cell by more sustained effort.

The *nature of the stimulation* is of some importance.

The convulsions are only elicited by stimulation of certain paths, *i. e.*, by direct stimulation of a nerve, and by the special senses of sight, hearing, and especially touch, the latter being by far the most active. Direct stimulation of an exposed muscle or of the intestine is very much less efficient than stimulation of the skin. No matter how slight the stimulation, if it has any result at all, it is always maximal.

The tetanizing action of strychnin being located in the spinal cord, several facts are explained. Thus, that strychnin convulsions are abolished by curare, since curare blocks impulses from the cord to the muscles. Also, that strychnin has a stronger action on a paralyzed limb in those cases of paralysis in which the lesion is above the cord, for cutting off of the spinal cord from the brain always increases its reflex excitability.

The fact that strychnin in small doses increases the *tone of muscles* is also due to its heightening the reflex excitability of the spinal cord. Not only the convulsive centers, but other spinal centers are put in a condition more favorable to reflexes. It is in this way that strychnin is useful in *impotence* or in *paralysis of the bladder or other sphincters*, when these are due to lowered activity of their respective spinal centers.

The increased activity of the muscles brings about several secondary results: (1) *Pain:* Strychnin convulsions are extremely painful, just as any other form of muscle cramp.

Patients and animals very often utter a *sharp cry* at the beginning of a convulsion. This is not due to the pain, but to the sudden contraction of the expiratory muscles, for it often precedes the convulsions.

(2) *Increased metabolism:* An increased consumption of oxygen and increased output of CO_2, and an increased use of glycogen. (3) Tendency to *rise of blood pressure.* (4) Tendency to *quickening of the pulse* (which is counteracted by the stimulation of the vagus center). (5) Tendency to increase of *temperature*, which is counteracted by the dilatation of the cutaneous vessels.

In small and young animals the heat-loss predominates, so that their temperature falls, especially when the dose is small. Large animals, on the other hand, show a rise in temperature. This holds true of all convulsant poisons.

(6) *Asphyxia* by tetanic fixation of the respiratory muscles (later, also by the depression of the respiratory center).

This asphyxia brings with it a venous condition of the blood and venous congestion of organs, lividity of the skin, protrusion of the eyeballs, dilated pupils, increase of the convulsions, and rise of blood pressure; later there is coma. Glycosuria is also a constant result of asphyxia. (Glycosuria also occurs on the intravenous injection of large quantities of isotonic salt solutions.)

The asphyxial stimulation of the vasomotor center is followed by paralysis from the same cause. In this way the aortic pressure falls below the point necessary to maintain the coronary circulation, the heart stops, and death results. The asphyxia is often the cause of, or at least contributory to, death; and life may be often prolonged by applying *artificial respiration*, even before the natural respiration has ceased. But this salutary effect of artificial respiration is also in part due to the increased destruction of strychnin which it favors.

For it not only saves an animal already in convulsions, but it may entirely prevent the latter if the proper dose is employed. It has a similar antidotal effect against the convulsions of brucin, caffein, and thebain, but not against those of picrotoxin or nicotin. (With strychnin the fatal dose is raised 50% if the animal is placed in an atmosphere of oxygen.) Certain experiments make it seem probable that the rhythmic movement of artificial respiration is also in itself beneficial.

2. The Medullary Centers.—There is a general stimulation and paralysis of the vagus, vasomotor, and respiratory centers. Stimulation of the *vagus center* finds its expression in a slowing of the pulse. This slowing is counteracted by the convulsions, for muscular motion of all kinds tends to produce quickening of the heart. The vagus center is also very rapidly fatigued.

The effect of strychnin upon the pulse is therefore somewhat variable. As a rule, at the beginning of a spasm, when the vagus center has become rested and the muscular action is not so violent, there is considerable slowing of the pulse, whereas there is a marked quickening toward the end of the spasm (Fig. 46, *A* and *B*).

The Vasomotor Center.—Strychnin produces the usual effects of stimulation of this center: viz., constriction of the arterioles of the abdominal area and dilatation of the vessels of the skin. Through the former, there is a rise of the blood pressure, which is further favored by the convulsions (Fig. 46, *A* and *B*).

It might be supposed that the rise of pressure was due solely to the convulsions, for a similar rise is observed in spasm however produced, but the effect of the strychnin is larger than can be accounted for in this manner, and,

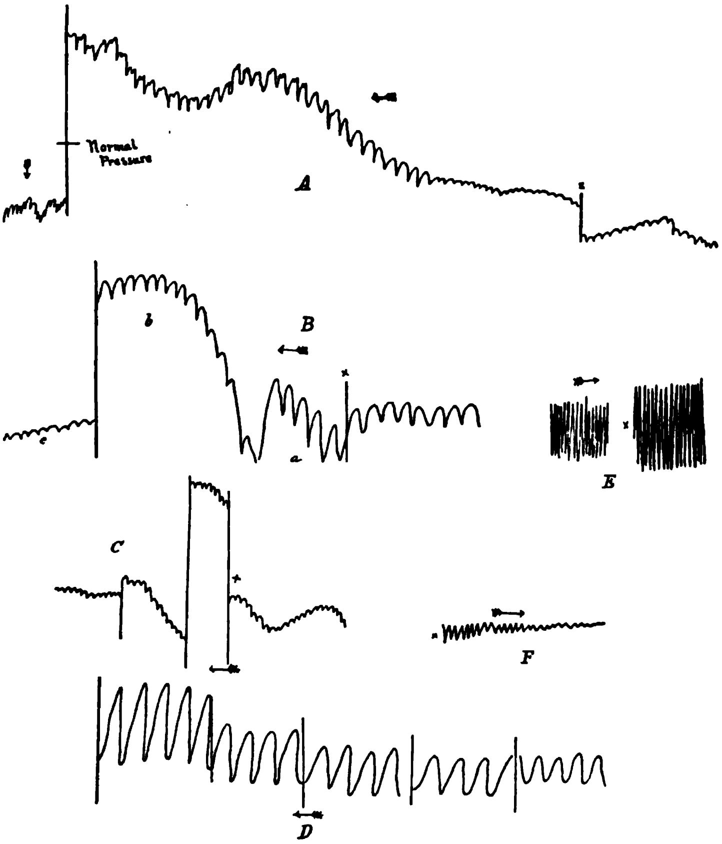


Fig. 46.—Effects of strychnin: The drug is injected at ×. *A*, *B*, and *C*, Carotid pressure tracings (dog). *A*, Shows vagus stimulation shortly after onset of spasm; rise of pressure notwithstanding slowing (vasoconstriction); strengthening of heart-beat (muscular spasm and slowing); at ↓ secondary quickening from vagus fatigue, and lowered pressure from vasomotor fatigue (central). *B*, Shows slowing and strengthening at onset (*a*); quick during height of spasm (*b*)= secondary to muscular; very quick and weak in interval (*c*), due to fatigue of vagus and vasomotor centers. *C*, Shows rise of pressure after *complete curare paralysis; i. e.*, direct vasomotor stimulation. *D*, Respiratory tracing, dog (tracheal cannula to tambour by T-piece). *E* and *F*, Tracings from isolated heart (after Hedbom): *E*, Stimulant effects; *F*, paralytic effects.

furthermore, strychnin causes a rise, although not quite as large, when the convulsions have been prevented by curare (Fig. 46, *c*).

The vasomotor center, like the other medullary centers, is soon fatigued by overstimulation and by asphyxia, and there is a fall of the pressure to below normal during the intervals of the convulsions (Fig. 46, *A*, *B*, and *C*).[1]

Small doses cause a rise of blood pressure and an increased tone of the heart without much change in the pulse-rate, partly through stimulation of the medullary center, partly through the increased activity—*i. e.*, tone—of the skeletal muscles. These doses need not be large enough to cause any fatigue of the center with depression of the circulation. Strychnin is, therefore, an extremely useful drug therapeutically, when it is desired to cause a quick rise of the blood pressure.

The Respiratory Center.—This is stimulated (Fig. 46, *D*) by strychnin both directly and reflexly through increase of muscular work.

The direct increase in the excitability of the respiratory center is very important therapeutically. The activity of this center is normally extremely variable, and as a result of disease—*e. g.*, asthma—or of drugs, the irritability of the center may be so depressed as to cause absolute failure of respiration. Strychnin removes this depression and enables the same stimuli to effect much larger results, and in this way tides over a danger.

The variable excitability of the respiratory center explains why the results obtained by faultless experiments are not always uniform. In fact, the useful stimulating effect of strychnin has been absolutely denied by some. But most experimenters and clinical observers agree that there is such a stimulation by strychnin and its group, as also by caffein, ammonia, atropin, and camphor.

It will be noticed that the effects of strychnin upon medullary centers are exactly the opposite of those produced by "shock" or by anesthetics (alcohol), and hence these form the mutual antidotal treatment. But care must be taken not to raise the dose of strychnin too high, or it will develop its paralyzing effects, which add themselves to those of the shock. It counteracts the effect of morphin on the medullary center, but is not the best antidote, since both stimulate the cord.

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[1] The spinal vasomotor centers are also stimulated, for injection of strychnin raises the pressure after section of the cervical cord. The existence of spinal respiratory centers is now denied.

Another use which can be made of the vasomotor stimulation is to relieve low blood pressure caused by *heart disease*. It could be used in this case only as a temporary expedient when immediate danger arises from this low blood pressure. Its permanent use would be precluded, since it increases the work which the heart must perform.

Strychnin is often called a "*heart stimulant.*" Its direct effect upon the heart is extremely small.

In experiments made on the excised mammalian heart, it has been found that a small dose slows the heart and increases its force. Somewhat larger doses cause a slight quickening, with increased force (Fig. 46, *E*). These effects are, however, probably too small to be of any therapeutic importance. Very large doses cause paralysis of the cardiac muscles (Fig. 46, *F*).

What therapeutists really mean by the statement that "strychnin stimulates the heart," is that it improves the pulse, a result of the rise of blood pressure, which, as has been said, is brought about by the stimulation of the vasomotor center. The term "cardiac stimulant" is one which has been used extensively, but so loosely that students will do well to discard it altogether.

The remedies which act similarly to strychnin on the vasomotor center are (besides the actual members of the group): Cytisin (from Cytisus and Ulex), Cornutin, Picrotoxin, and Coriamyrtin. None of these have any advantage over strychnin, and can be dispensed with.

Paralytic Effects.—The paralysis of the medullary center and spinal cord is partly masked by the convulsions, but shows in the intervals and toward the end. It is the usual cause of death in mammals, unless this takes place during respiratory spasms. It is due to cardiac depression, exhaustion, asphyxia, and a direct depressing action on the nerve centers.

There seems considerable reason to believe that in the frog the paralysis of the central nervous system is caused largely by the failure of the circulation through cardiac paralysis, but this is not the sole cause, for the heart is often still beating when the reflexes have disappeared. In the case of mammals death usually occurs before their heart has stopped.

It is important to bear in mind that the convulsions are not the dangerous element in strychnin-poisoning, but the paralysis.

Tetanus alone is not such a dangerous condition. Thus, tetanus quite as violent as that of strychnin has been produced, *e. g.*, by camphor, without being fatal, and the very severe convulsions of traumatic tetanus may last for weeks, whereas large doses of strychnin may kill after a single twitch or even without any signs of convulsions (death may then, however, be due to cardiac paralysis).

This is of great therapeutic importance, since it teaches that remedial measures must be directed not so much against the convulsions, as against the subsequent paralysis.

3. The effects upon the **brain** have not been sufficiently investigated. This much is certain, that they are not very great. There is no evidence that the *motor psychic areas* are more excitable. Consciousness is not lost until the asphyxial coma.

Among the **special senses** there is a well-marked *increase in the sharpness and field of vision for all colors*, in the olfactory sense, and in the sense of touch.

In the last two the action is entirely central. The effect on vision is, however, largely through an action on the retinal ganglia cells.

(B) **Peripheral Actions.**—It has *no action on nerve-fibers, nor striped nor unstriped muscle, nor sensory end-organs.* Very large doses, however, lessen the excitability of the latter in the frog. It has a curare action on the endings of striped muscles.

This may be seen in the frog, but it develops too late to show in mammals. Both strychnin and brucin paralyze the superior cervical ganglion. It has not been investigated whether this extends as well to the other sympathetic ganglia. The effect upon the heart has already been mentioned. Whether this effect is on the muscle-fibers or nerve endings cannot now be stated.

Alimentary Canal.—Strychnin is often of great benefit in chronic gastric and intestinal catarrh. It shares this action with all other bitter substances. No definite explanation can be furnished. It has been suggested that there are in the lower portion of the alimentary canal, organs corresponding in function to the taste-buds, and that " bitters " aid digestion through reflex stimulation started in these organs. For this local effect, the Galenic preparations of nux vomica are superior to the pure alkaloid, since they are not so quickly absorbed.

The effects of strychnin upon animals devoid of a central nervous system have not been sufficiently studied. All those possessing nervous structures are affected by it.

IV. ABSORPTION, ETC.

Strychnin is readily and quickly absorbed, mainly from the intestine. It is probable that the stomach partakes in the absorption in man, although this is not the case in the rabbit. The **excretion** begins quickly, but lasts for a long time (over eight days). It takes place by sweat, saliva, bile, and especially urine.

Fate.—The excreted strychnin is unchanged. Part of the poison, however, undergoes destruction, probably oxidation, in the body. The poison is retained for a long time in the liver and central nervous system. The destruction of strychnin has already been discussed in the introductory chapter, page 135.

The action of strychnin is influenced to a marked extent by the temperature of the animal. Cooling lessens the tetanus but increases the toxicity.

V. DIFFERENCES IN MEMBERS OF THE SERIES.

Brucin is very much weaker than strychnin. It also shows a greater tendency to paralysis of the central nervous system and greater curare action. It is, therefore, much less useful therapeutically. Thebain and the other members are not used.

Toxin Tetanus.—

The effects of traumatic tetanus do not result directly from bacteria, but from their toxic products. Several of these have been isolated, belonging to the ptomains and toxalbumins. The most important, however, is a toxin.

Toxins (toxalbumins of Brieger) are the usual disease factors in infections. When pure, they do not give the biuret reaction, or at most very faintly. They are not, therefore, proteids. Nor do they show the basic character of alkaloids. Since they may be developed in non-proteid media, they cannot be looked upon as decomposition products of proteids. They are, however, probably nitrogenous. They have never been produced synthetically, and are formed exclusively by bacterial action.

The tetanus toxin affects the central nervous system *precisely in the same way as strychnin.* The location of the tetanus in the spinal cord is the same. It is possible, however, that the toxic tetanus consists in direct stimulation rather than in an increase of the reflex irritability of the cord. This has not been well made out. The most conspicuous difference consists in the existence of a long latent period and in a different channel of absorption. Strychnin tetanus begins just as soon as the poison is injected, the convulsions involving all the muscles, irrespective of the place of application. The absorption may occur by either blood or lymph channels. Toxin tetanus, on the other hand, shows three stages: (1) Local spasms: There is a contracture limited by the inoculated area; *e. g.*, the leg. (2) This local contracture spreads to adjoining structures. (3) The spasms become generalized.

This is the usual course in animals; but in man and the horse a trismus is usually the first symptom. If the poison is injected intravenously, the spasms are generalized from the start in all animals.

The question naturally suggests itself: If the poison acts on the central nervous system, how does it happen that the contracture at the place of injection precedes the general convulsions, or in many cases may remain local for weeks without becoming general at all? One might think that the irritation from the wound, acting as a reflex stimulus, might be responsible for the local condition. This is, however, not the case, for a much stronger irritation applied by croton oil at another point does not produce localized contracture at this area. The only plausible explanation is that the poison is conducted to the central nervous system along the nerves. The nerve sheath is quite capable of conducting injection masses, and it has been shown that the portion of the central nervous system corresponding to the entrance of the nerve coming from the affected area is richest in toxin. It has also been shown that the introduction of the poison into the subdural space causes local tetanus of the corresponding area, which by careful application may even be confined to the corresponding side.

When the poison is injected intravenously, it disappears very rapidly from the blood (inside of four minutes), but does not produce its action for quite a long time. From this, it would appear that the poison is fixed in some way in the tissues, or particularly in the central nervous system, since it is from here that the symptoms arise; and according to the theory of nerve conduction, it would be fixed primarily in those portions which it reaches first. It has indeed been shown that the spinal cord may contain tetanus toxins, whilst the blood may at the same time be free from them. The modifications produced by it must, then, occur very slowly, and they can be restrained for a time by suitable conditions. In cooled frogs it may be injected without producing any symptoms whatsoever, and we know that it is not destroyed, but retained somewhere, for the tetanus can be produced at any time up to several months by raising the temperature of the animal. Similarly, the contracture may persist in mammals for several weeks after the toxin has disappeared from the blood.

It still remains to be demonstrated by experiments, which would not seem to be so very difficult, whether the poison in these cases is fixed and retained in the central nervous system or whether it has led to an alteration of its function which may persist or become conspicuous only after the poison itself has been excreted.

The tetanus *antitoxin* acts chemically, *i. e.*, it must come into actual contact with the toxin and may destroy the latter outside the body.

Since the toxin is absorbed but slowly, the antitoxin should be injected at the seat of inoculation, on the chance that it will neutralize the toxin as it is formed. When the poison has once reached the central nervous system, the antitoxin has little action—probably because it is absorbed by different channels and does not reach the spinal cord in sufficient amount.

This is borne out by clinical result: after the symptoms have appeared, the serum treatment is useless. It is very useful, however, as a prophylactic, and should be used in all cases as soon as possible after a suspicious injury has been received. The introduction of the antitoxin into the subdural space has not been as successful as was anticipated. The reason for this lies in the fact that it passes very rapidly into the blood and lymph, so that this manner of administration does not bring it more directly into contact with the spinal cord than when it is injected elsewhere.

One might be tempted to suppose that with this and other toxins showing a latent period, it is not the injected substance which is active, but that this leads to the generation of the really active body during this latent period. If this is the case, this "secondary toxin" must be developed in and confined to, the central nervous system itself, for it does not exist in the blood at the time of the attack. (Similarly, the blood contains no toxic substance in diphtheria at the time when the toxic symptoms appear.)

Like all other toxins, this tetanus poison is destroyed by ferments, and is therefore ineffectual by the mouth.

Relation to Other Groups.—By its action on the central nervous system, strychnin resembles *caffein* and *picrotoxin*, the difference consisting in the portion of the central nervous system mainly affected. The increased irritability of the spinal cord connects it with *morphin*, its action on the endings of the striped muscle with *curare*. (A derivative of strychnin, methyl-strychnin, is a member of the curare group.) The action on the cervical sympathetic ganglion is allied to that of *nicotin*. The cardiac paralysis is common to many poisons.

VI. TOXICOLOGY.

Strychnin is one of the most commonly used of poisons both for suicidal and criminal purposes.

In a statistical collection of *all kinds of poisoning*, the order of frequency is the following: opiates, cyanids, vermin and fly killer, carbolic acid, strychnin, mineral acids, oxalic acid, arsenic, mercury, phosphorus, chloroform and chloral, ammonia, belladonna, aconite, copper, and iodin. In *criminal poisoning* it runs: arsenic, phosphorus, copper, mineral acids, cantharidis, strychnin, opiates, mercury, cyanids, and iodin.

It might at first appear strange that a substance with such a marked and disagreeable taste as has strychnin should be used for poisoning, but a moment's thought will show that if a liquid is taken unsuspectingly the taste is not noticed until a large amount has been swallowed.

It is a remarkable fact that women suicides have a much greater leaning than men to poisoning, this forming 11% of the cases of suicide in the former, and 5% in the latter sex.

Time of Appearance of Symptoms.—The symptoms do not often appear before fifteen minutes, nor are they often delayed beyond half an hour, but in one case an hour and three-quarters elapsed before the symptoms began. The time will depend upon individual differences, upon the manner of introduction,—if into the stomach, whether this is full or empty, and upon the nature of the food, if any is present,—upon the place of introduction (hypodermically, etc.), and upon the preparation of the poison employed. The alkaloid will act faster than the tincture, and these, again, faster than pills.

First Symptoms.—The symptoms may start with a feeling of uneasiness and a heightened reflex irritability (nervousness); then comes a sensation of tightening and drawing in the lower jaw, or there may be a twitching of the little finger. These symptoms are the most that should be produced with therapeutic application.

In case any portion of the body is paralyzed from a high lesion, this part may be the first to show the spasms.

Advanced Symptoms.—With large doses these prodromal symptoms are usually absent, and the attack often begins suddenly, with a cry or shriek, which is usually caused mechanically by convulsive movements rather than by pain. This is followed very quickly by the characteristic convulsions. The patient is thrown into general convulsions, at first clonic and then tonic. Opisthotonos results from the contraction of the extensors. The patient will touch the ground with his head and feet, the rest of the body being arched above the floor. The feet are curved inward. These conditions do not persist, but pass into clonic spasms and soon an intermission ensues.

The respiration during the attack is at first labored and dyspneic, and then ceases by the spasmodic contraction of the diaphragm. The abdomen and chest may become as stiff as a board. The patient may foam at the mouth on account of the disturbed respiration. The interference with the circulation and the pressure on the abdominal viscera, aided by the stimulation of the respective medullary centers, may lead to purging and vomiting. Lock-jaw and risus sardonicus may occur later. The interference with the respiration leads to asphyxia, and this to cyanosis, dilatation of the pupils, and later coma. The pulse is small and tense. The patient is perfectly conscious and usually suffers excruciating pain. In a few cases this may be absent on account of the anesthetic effects of asphyxia.

These spasms are interrupted by ***intermissions***, during which the stimulation symptoms disappear entirely and are supplanted by general depression. Suddenly the attack is repeated as before. The number of seizures is variable. Three or four are usually fatal. The duration of the spasms and of the intervals differs according to the severity of the poisoning. They become shorter toward death.

Death.—The patient dies in ten to thirty minutes after the first attack, either during a spasm or in the interval: if the former, through fixation of the respiratory muscles; if the latter, through paralysis of the medullary centers. Death by strychnin is characterized by early and often persistent rigor. (This is common to all forms of convulsions.) The postmortem appearances are those of asphyxia and violent convulsions: venous congestion, often hyperemia of the central nervous system, and small hemorrhages; in a few cases hyperemia of the alimentary tract.

Differential Diagnosis of Strychnin-poisoning.—Strychnin tetanus may be confused with traumatic tetanus, spinal meningitis, epilepsy, or hysteria. *Traumatic tetanus* is characterized by previous malaise and slow development. The convulsions begin in the jaw. The muscles remain rigid in the intermissions. The course is comparatively slow. Strychnin tetanus may also begin in the jaw, but not as markedly. In rare cases of strychnin poisoning the muscles also preserve their rigidity during the interval, so that the diagnosis is sometimes impossible. When in doubt, strychnin treatment should be used, as it is beneficial in all similar conditions. The course of the case will clear up the diagnosis.

In *spinal meningitis* the diagnosis may be made by the fever and history, and signs of injury to the vertebræ can generally be discovered. *Epilepsy* differs by the loss of consciousness; the reflexes are normal. In certain cases of *hysteria* the diagnosis may be impossible. Such cases should also be treated as for strychnin.

Toxicity for Different Animals.—Snails are almost immune. For other animals the scale runs as follows (these are the smallest fatal doses in milligrams per kilo on subcutaneous administration):

	Blythe.	Sollmann.
Rabbits	0.5	
Man and dog	2.0	
Mouse	2.4	
Guinea-pig		4.5
Frog[1]		5.5
Snake	23.0	

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[1] With the frog, the spasms appear with one-sixth the fatal dose; with the guinea, they only set in when at least 95% of the fatal dose has been given.

Children are comparatively insusceptible, whereas it is a dangerous poison for old people, on account of the frequent existence of atheroma or fatty heart, leading to rupture through the increased blood-pressure.

Treatment of Strychnin-poisoning.—*Chemic and Emetic.*—This must be very prompt on account of the rapid absorption.

Chemic: Here permanganate of potash or iodin form the ideal antidotes, because with them it is not so necessary to evacuate the stomach. In the absence of these, tannin may be given, but, if possible, coffee or tea should be avoided, since the caffein in these adds to the stimulation of the central nervous system.

Evacuation of the stomach: It is difficult to make a general statement as to whether an emetic or the stomach-pump should be employed. If the spasms are very violent, they certainly should not be, for either will suffice to start the spasms, and emetics are also objectionable because of their depressing effect. So that, if evacuation is considered advisable the tube is preferred, also because it is so much quicker. With this, a chemic antidote should, of course, be added to the wash-water. It is doubtful whether either measure is very useful when fatal doses have been taken, because, by the time the physician can arrive, sufficient of the poison is probably absorbed to render evacuation useless. However, if the convulsions are mild at this time, these measures may be used to relieve the anxiety of the patient, if nothing more. They should never be employed if the patient struggles against them.

For *physiologic treatment*, the most useful antidotes are the members of the group of hydrocarbon narcotics: chloral, paraldehyd, or chloroform. They have all been advised. Chloral is given in doses of 2 Gm. (½ drachm), with the addition of another gram (15 grains) after half an hour or longer, as necessary. There is always the danger in giving this, that its paralytic effects may coincide with those of the strychnin, and thus increase the danger. For this reason *chloroform* is considered the best, since its action can be very largely controlled. *Morphin* should be avoided, and only used in emergency. Its effect upon the brain is, of course, antidotal to the strychnin, but this is of little importance, and on the other hand, it is likely to increase the reflex excitability of the spinal cord and thus add its effect to that of strychnin. Its depressing action on the respiration is also certainly undesirable. Nicotin was at one time recommended, but thorough tests have shown that it is useless, as might well be predicted from its action.

Artificial respiration, as well as the inhalation of oxygen, should be begun early, since this has been proved to be a most efficient treatment.

It is claimed as a result of animal experiments that the application of external heat decreases the mortality.

The *fatal dose* is stated as ½ to 1½ grains, the former being the smallest fatal quantity recorded, but $\frac{1}{12}$ grain in a woman has given violent results. However, even 4 grains have been recovered from in cases where appropriate treatment was used.

VII. THERAPEUTICS.

The principal effect of strychnin is upon the **spinal centers,** and this is made use of in various ways:

1. *General Tonic.*—Its tonic effect may be explained in two ways. First, by its producing an increase in the muscular tone. This increase of tone produces a more healthy feeling in the patient. Secondly, its effect upon the alimentary canal improves the appetite and digestion.

Consequently strychnin as a tonic should be given in the form of the preparations of nux vomica, the tincture being especially desirable. It is used in this way against marasmus, tuberculosis, chronic gastric or intestinal catarrh, etc.

2. *Paralytic Disorders.*—We repeat that strychnin only increases the excitability of existing structures. It cannot, therefore, be of any use in organic lesions of the cord. It may be of use in *functional* lowering of the activity of the cord,—*e. g.*, lead-poisoning, or sometimes in diphtheritic paralysis. It is especially useful in nervous lesions above the cord;

For, by stimulating the latter, it will preserve the tone, and, consequently, the nutrition of the muscles, and in this way may temporarily prevent their atrophy while the higher lesion is being repaired. For this purpose it will give the best results when used conjointly with massage and electricity. In some way it also lessens the pain in older paralyses.

3. *Other Reflex Spinal Centers.*—The lower centers of the cord, especially the sphincters of the bladder and rectum, are put into better condition by strychnin, and it is, therefore, useful in certain forms of incontinence of the feces and urine.

Incontinence of the urine may also be due to overaction of the detrusor urini, in which case atropin would be indicated.

The stimulation of the spinal cord also explains its effects in impotence.

4. The stimulating effect of strychnin upon the **medullary centers** is one of its most useful actions; *e. g.*, in shock.

Shock and collapse cause, or are caused by, depression of the medullary centers, and are characterized by quickened pulse, lowered blood pressure, slow and shallow respiration, *i. e.*, paralysis of the vagus, vasomotor, and respiratory centers. Strychnin stimulates precisely these structures, and is, therefore, an ideal treatment. We may count under such conditions the following: traumatic and surgical shock, poisoning by alcohol-narcotics, carbolic acid and the antipyrin series, etc.

Certain *snake venoms* also act by depression of the medullary centers (see Chap. XVIII), and strychnin is reported to give good results in their treatment. This is, however, not a new fact, for Plenck (1785) mentions that it is used by the natives of Ceylon for this purpose.

Strychnin is not so useful against depression by morphin-poisoning, for the same reason that prohibits morphin as an antidote in strychnin.

Those who regard sea-sickness as a collapse condition, have also employed it here, but its benefits are doubtful.

5. The useful effect of *strychnin* in acute *alcoholic poisoning* has suggested its employment in the chronic form.

Its usefulness here will vary according as to whether there is increased or diminished excitability of the cord, either of which may exist. In the latter case it is indicated, both on account of the greater relaxation of the muscles and the gastritis. In the former it would be useful only as an appetizer, an effect which may be attained equally well by simple bitters (see Chap. XXX, A) without further increasing the spinal irritability.

6. Its effect upon the *vasomotor center* causes it to be used in all conditions where bad effects are produced by low blood pressure.

We have already referred to the limitations to its use in *heart disease* when discussing its effects upon the circulation.

It is also used in cases where the nervous mechanism of the circulation is locally unbalanced; *e. g.*, hemicrania. It is possible also that its beneficial effects in asthma may be partly accounted for in this manner. It is, of course, indicated in any case of *vasomotor paralysis*.

7. Its very pronounced stimulation of the *respiratory center* indicates its use in all cases of respiratory failure, whether by direct depression or by fatigue of the center. When death seems imminent, it is justifiable to push the strychnin until twitching of the finger-tips occurs. It should never be

continued beyond this stage, for the danger of producing strychnin paralysis is great.

We need only allude to the use of strychnin in *diminished visual activity*. It undoubtedly improves this, but its effects are only temporary.

A dose of 2 to 3 mg. is required to produce this effect. The action may also be obtained by the application of a 1% solution to the cornea.

On the whole, *strychnin must be looked upon only as a temporary remedy*. It must be remembered that it does not in any way permanently improve the condition of the central nervous system, nor does it increase any of the functions except the reflex irritability. It is doubtful whether the permanent maintenance of this artificially raised irritability is ever of benefit. But that its temporary action in bridging over the time required for reparative processes is extremely useful, belongs to the best established facts of modern therapeutics.

VIII. MATERIA MEDICA.[1]

Nux Vomica.—The seed of *Strychnos Nux Vomica*, Loganiaceæ, East Indies.

Alkaloids (2.5% to 5%): Strychnin, 0.2% to 0.6%.
Brucin, 0.5% to 1.0%.
Tannin, fat, gum.
Dose: 0.03 to 0.3 Gm. (½ to 5 grs.).

Preparations (all miscible with water or alcohol. Made with three-quarter alcohol and acidulated):
⁂ *Tinctura Nucis Vomicæ*, U.S.P.: 2% extract = 0.3% alkaloids. B.P.: 0.22% alkaloids. *Dose:* 0.3 to 1.2 c.c. (5 to 20 ♏).
Extractum Nucis Vomicæ Fluidum, U.S.P.: 1.5% alkaloids. *Dose:* 0.05 to 0.25 c.c. (1 to 4 ♏).
Extractum Nucis Vomicæ, U.S.P. and B.P.: 15% alkaloids. *Dose:* 0.01 to 0.06 Gm. (⅙ to 1 gr.).

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* **Ignatia.**—The seed of Strychnos Ignatia, Philippines.

Strychnin, 0.5% to 1.5%.
Brucin, 0.5% to 1.4%.
Tannin, fat, gum.
Dose: 0.03 to 0.2 Gm. (½ to 3 grs.).

Preparations (alcohol, eight-ninths; miscible with water and alcohol):
* *Tinctura Ignatiæ*, U.S.P., '80: 10%. *Dose:* 0.3 to 1.5 c.c. (5 to 25 ♏).

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[1] The most important preparations are marked with triple asterisk ⁂. Single asterisk = not official.

Strychnin.—Alkaloid derived from plants of the family Loganiaceæ. Very bitter (1 : 50,000).

Alkaloid, U.S.P., B.P. : Soluble in 7000 water, 110 alcohol.
⁂ *Sulphate*, U.S.P., B.P. : Soluble in 50 water, 110 alcohol. *Dose :* 1 to 5 mg. ($\frac{1}{60}$ to $\frac{1}{12}$ gr.).
Nitrate, Soluble in 60 water.
Hydrochlorid, B.P. : Soluble in 50 water.

Preparations :

Ferri et Strychninæ Citras (U.S.P.) : 1% strychnin. *Dose :* 0.06 to 0.3 Gm. (1 to 5 grs.).
Liquor Strychnini Hydrochloridi (B.P.) : (1%.) *Dose :* 0.1 to 0.5 c.c. (2 to 8 ♏).
Syrupus Ferri, Quininæ et Strychninæ Phosphatum (U.S.P.) :
Dose = 4 c.c. = ʒj = quinin 0.12 Gm.
strychnin 0.8 mg.
⁂ *Elixir Cinchonæ, Ferri et Strychninæ*, N.F.
Dose = 4 c.c. = ʒj = Strychnin, 0.7 mg.
Cinchona alkaloids, 0.1 Gm.
Iron phosphate, 0.1 Gm.

All other elixirs of N.F. containing strychnin have the same proportion.
* *Liquor Strychninæ Acetatis*, N.F. (Hall's solution) : 0.2% (acidulated).

Brucin.—*Dose :* 0.05 Gm. (¾ gr.).

(B) CAFFEIN GROUP.

I. MEMBERS.

The members of this group are chemic derivatives of xanthin. They are found in certain plants, and occur also as waste products of metabolism in muscles and other organs, appearing in the urine and feces. The principal ones are :

Hypoxanthin, $C_5H_4N_4O$.
Xanthin, $C_5H_4N_4O_2$. { Di-methyl-xanthin, $CH_2(CH_3)_2N_4O_2$.
Methyl-xanthin, $C_5H_3CH_3N_4O_2$.
Tri-methyl-xanthin, $C_5H(CH_3)_3N_4O_2$.
Uric acid, $C_5H_4N_4O_3$.
Guanin, $C_5H_5N_5O$.
Adenin, $C_5H_5N_5$.
Creatin, $C_4H_9N_3O_2$ (— H_2O =) Creatinin, $C_4H_7N_3O$.

The methyl-xanthins occur in isomeric form, the most important compounds being :

Mono-methyl-xanthin : Heteroxanthin (human urine).
Di-methyl-xanthin : { Theobromin (in cacao).
Theophyllin (in tea).
Paraxanthin (in human urine).
Tri-methyl-xanthin : Caffein (thein).

These bodies, in so far as they are formed in living tissue by retrograde metamorphosis or by fermentative changes,

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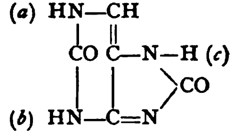
The most important preparations are marked with triple asterisk ⁂.
* Not official.

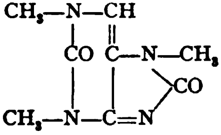
other than bacterial, are termed *leucomains*. They are also included under the term "*purin bases.*"

The constitutional formulas will serve to show their relation:

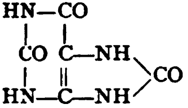
XANTHIN.



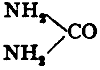
CAFFEIN.



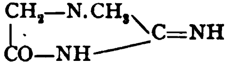
URIC ACID.



UREA.



CREATININ.



As far as soluble, they all show to a greater or less extent the typical caffein actions, especially those on muscle and kidney. This group has, therefore, a physiologic as well as a pharmacologic importance, since it tends to explain the phenomena of fatigue, diuresis, etc.

The therapeutically most important members, caffein and theobromin, are found in plants of at least six families, which are scattered over many portions of the globe, and have usually been discovered and consumed by the natives. A list of the most important will be found under the materia medica (p. 189).

II. SUMMARY OF ACTIONS.

1. Increase of the reflex irritability of the central nervous system from above downward, leading to a stimulation of the psychic area, then of the vasomotor and respiratory centers, and later to heightened reflexes and tetanic convulsions. In large doses this stimulation is followed by paralysis.
2. Increased ease of muscular contraction, leading to loss of elasticity and to rigor (with skeletal and cardiac muscles).
3. Direct stimulation of the renal epithelium.

III. DETAILS OF ACTION.

(A) Central Nervous System.—**1.** The members of the series lead to a heightening of nervous activity, first shown in the **higher psychic functions.** This is most prominent with caffein, other members showing a more conspicuous paralysis.

There is a clearer and quicker flow of thought, disappearance of drowsiness, more sustained intellectual effort, more efficient appreciation of sensory influences of all kinds, especially in fatigue, and more perfect association of ideas.[1]

With larger doses (0.5 to 1.5 Gm.) this passes into wakefulness and restlessness, vertigo, headache, and tinnitus aurium. In extremely large doses this may pass into delirium, and finally coma.

In lower mammals the cerebral effect is shown by restlessness. In the frog there are no symptoms referable to the brain.

2. **Medulla.**—This is also stimulated by caffein in a manner similar to strychnin, except that the vagus stimulation is very slight as compared with that of the vasomotor and respiratory centers.

The *vasomotor stimulation* results in a rise of blood pressure (Fig. 47, *A*).

The vasoconstriction is shown by the diminished size of the organs and comparatively low venous and high arterial pressure. That the seat of the stimulation is central can be demonstrated by the fact that caffein constriction is very largely interfered with by chloral, which paralyzes the vasomotor center. That the rise of pressure is not due to an increased cardiac action is shown by its absence in preparations of the isolated mammalian heart. Since the rise occurs after curare, it is not muscular.

This action on the vasomotor center is *not nearly so great as in the case of strychnin.* It cannot be produced nearly so promptly, and the doses required are so large that they will produce other unpleasant effects.

Very large doses produce paralysis of the vasomotor center, and consequently a fall of blood pressure. (Fig. 47, *B*).

The *vagus center* is very little affected (Fig. 47, *A* and *B*).

Respiratory Center.—The effects of caffein upon the respiratory center resemble those of strychnin, there being first quickening and then paralysis.

3. **Spinal Cord.**—The effects upon the spinal cord also resemble strychnin, except that they are very much smaller and occur only with relatively large doses. There is the same increased reflex irritability, then tremors, and finally

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[1] These are the centers first paralyzed by alcohol and to some degree by morphin and cannabis. Caffein is, therefore, an efficient antidote for these, and especially alcohol, since the medullary and spinal effects are also antagonistic, whereas strychnin is antidotal only in its medullary action, but heightens the spinal effect.

tetanus. This tetanus shows the same intermittent character as that of strychnin, and also involves the respiratory muscles in the same manner. It occurs both in mammals and frogs.

There is a difference in the reaction of *different species of frogs* to caffein. The esculenta is thrown into typical tetanus, whereas the temporaria goes primarily into rigor. The distinction is, however, quantitative rather than qualitative, since large doses will cause primary rigor in the esculenta also.

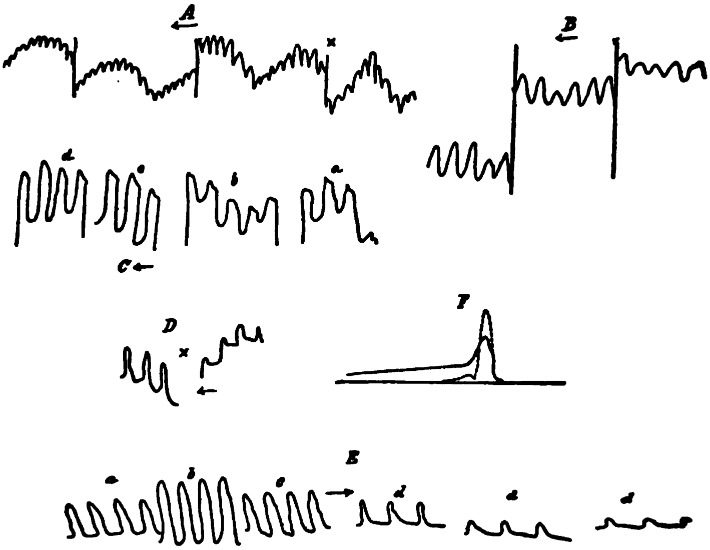

Fig. 47.—Caffein: The action of the drug begins at ×. *A* and *B*, Carotid pressure, dog: *A* shows vasomotor stimulation, *B* paralysis. *C* and *D*, Cardiomyogram, dog; upstroke = systole: *C*, *a*, normal; *b*, immediately after caffein—the beats are smaller, the rate slightly quickened, systole lengthened; *c*, two minutes after caffein—the force is increased; *d*, four minutes after caffein. *D*, 6 c.c. 1 : 1000 caffein intravenously: The force is increased, diastolic pause lessened; the rate and blood pressure were unchanged. *E*, Tracing from frog's heart; upstroke = systole: *a*, normal; *b*, 1 : 10,000 caffein; *c*, 1 : 1000 caffein; *d*, successive tracings with 1 : 100 caffein. *F*, Tracing from frog's muscle: dotted line = 4 : 10,000 caffein; solid line = 4 : 1000 caffein.

It rests upon a greater tendency to rigor existing in the muscles of the temporaria, for these are also more subject to other forms of rigor.

Caffein is, therefore, a striking illustration of the different effects which may be observed on the intact animal, since it may produce in frogs death in three different ways according to the strength and manner of its administration: The frog may die without any symptoms, through total collapse from cardiac paralysis, or it may be thrown into spasms through the stimulation of the spinal cord, or it may be overtaken by rigor through the action on the muscles.

The *tetanus*, like that of strychnin, is located in the spinal cord.

This tetanus is the only symptom with frogs. The dose required for mammals is considerably larger than that necessary to give a vasomotor, cardiac, or diuretic effect. Whereas for the latter 20 mg. per kilo are ample, 20 mg. will only cause tremors, and convulsions will not develop until 80 mg. have been given. Still larger doses paralyze the heart or the whole central nervous system.

In the intact frog the paralysis of the cord is obscured by the rigor. It can be demonstrated by ligating a leg exclusive of the nerve, when caffein will destroy its reflexes, although the muscles are still excitable.

(B) The Effect on Skeletal Muscles.—Small doses increase the excitability of the muscles, so that a lesser stimulation will suffice to produce a contraction. It also increases the quickness and height of the contraction and the maximum load which the muscle is capable of lifting. Somewhat larger doses have the opposite effect (Fig. 47, *F*). This is shown in a lengthening of the contraction very similar to that produced by fatigue; *i. e.*, the lengthening shows at first in the relaxation, later in the contraction as well. The other phenomena of fatigue are also present: The height of the contraction is less, the maximal load is smaller, and the muscle is exhausted more quickly by tetanus than is a normal muscle.

The contraction then becomes smaller and smaller, and the muscle gradually passes into rigor.

This increase and diminution of the functions bears so striking a resemblance to the phenomena of work and fatigue as to suggest a connection between the two. It is possible, although not demonstrated, that fatigue is partly due to an accumulation of xanthin products.

The *rigor* resembles that of rigor mortis in all respects: The muscle is hard, opaque, granular on microscopic examination, acid to litmus paper, etc.

This rigor may be produced in living animals by injection of sufficiently concentrated solutions, as also by chloroform and a few other substances.

All of these favor the clotting of muscle-extract. It will not do, however, to accept the latter as the explanation of the rigor, for many other substances produce clotting of the extracts with even greater readiness, but do not produce the rigor.

The effect of caffein upon smooth muscles needs investigation.

The effect upon **cardiac muscle** is essentially the same as that upon skeletal muscle.

The heart muscle is, however, somewhat more resistant than the skeletal, for the heart of the frog is still found beating after the other muscles have gone into rigor.

With the frog's heart (Fig. 47, *E*) *small doses* increase the absolute strength of contraction and the volume of blood thrown out in a given time. The duration of the systole is increased at the expense of the diastole. The rate is somewhat quickened, but this is soon replaced by slowing. The heart becomes permanently more and more contracted, finally reaches standstill, generally in systole, and then goes into rigor. The standstill is sometimes in diastole.

The analogy of these phenomena to those of skeletal muscles is most apparent.

The effect upon the isolated *mammalian heart:* In intact mammals, the most conspicuous symptom on the part of the circulation is progressive increase of the pulse-rate, occurring even with small doses, and increasing further with each additional injection. Since this occurs in a heart excised from the chest, the action is peripheral. It also occurs after atropin, and cannot, therefore, be due to any inhibition of the vagus mechanism. It must be either muscular or accelerator stimulation. It is at present impossible to decide definitely between these. The power of the muscle as shown by the amplitude of the excursion and the height of the intracardiac pressure is sometimes diminished, sometimes increased (Fig. 47, *C* and *D*). A diminution would point to the stimulation of the accelerators rather than of the muscle-fibers.

Probably the latter plays, however, some rôle, for a quickening is seen in the heart of the embryonic chick, before nerve-fibers have become developed.

The lessened efficiency must be due to a direct effect upon the muscle-fibers. It is probably caused by a diminished elasticity, since it can be removed by drugs like strophanthus. The use of caffein for stimulating the heart is, therefore, irrational. It cannot be said to have any useful action upon the circulation except that which may be obtained in more powerful form by strychnin. In the intact animal there is usually a quickening, and with larger doses a slowing.

The details which are seen on the cardiomyogram are quite variable. There may be:

1. Quickening, with relation of systole and diastole unchanged.
2. Quickening, with systole longer than diastole.
3. Quickening, with systole relatively shorter.
4. Slowing of both phases.

The larger doses render the heart irregular and produce in man *palpitation* and distress. Death occurs through cardiac paralysis with diastolic standstill. It may take place at once, and with practically no other symptoms, if the dose has been very large.

The irregularity of the heart leads to a fall of *blood pressure*, which is aided by the vasomotor paralysis obtained in this stage (Fig. 47, *B*).

(C) **The Effect upon Metabolism.**—Caffein causes a slight *rise of temperature*, partly by its action on the central nervous system, and especially by its direct muscular effects. In consequence of this, it also increases the metabolism—*i. e.*, the production of urea and CO_2. The older statements that it lessens metabolism are erroneous.

(D) **The Effect upon the Kidneys.**—Under certain conditions caffein, and especially the other members of the series, may cause a considerable increase in the secretion of urine.

This was at first attributed to a stimulation of the heart muscle, similar to digitalis, but, as has been shown, the heart is rather weakened. Nor is it dependent upon a rise of blood pressure, for the stimulation of the vasomotor center by caffein also causes a constriction of the renal vessels which always diminishes, and may inhibit, the secretion of urine.

The effect must, therefore, be exerted *directly upon the kidney cells*. Unless counteracted by its effects on the vasomotor center, this tends to produce a dilatation of the renal vessels. The diuresis is produced by doses smaller than those required for any other effect, and since it is interfered with by vasomotor constriction, it is better to give the caffein in very small doses.

Although the increase in watery secretion has been noted for a long time, the changes in the other constituents have been very little studied. The only statement in regard to this matter is, that the excretion of alkalies, and especially sodium, is increased even out of proportion to the diuresis.

Caffein, so far as known, has no effect on *other gland cells*, nor upon *muscle-nerve endings*, nor upon *ganglia*.

Caffein causes a peculiar vacuolization and condensation in the protoplasm of the ameba and other infusoria, due probably to its basic nature.

IV. ABSORPTION, FATE, EXCRETION.

Caffein is rapidly absorbed. In its passage through the body it undergoes changes, only a small part being excreted unaltered.

The change consists largely in the loss of methyl groups, the caffein (tri-methyl-xanthin) being converted into di- and mono-methyl-xanthins. Only 30% to 40% are excreted in this way. On account of the similar composition one might be tempted to suppose that the rest of the caffein is converted into uric acid. This is, however, not the case, the oxidation being more complete and probably reaching urea. Of the other members of the series, theobromin suffers a similar fate, but a larger percentage is excreted unchanged. The greater part leaves as heteroxanthin. Hypoxanthin and xanthin are excreted largely as uric acid.

V. DIFFERENCES IN THE MEMBERS OF THE GROUP.

Of these, caffein has the strongest *stimulating effects* upon the central nervous system. With theobromin this is very small. (Caffein should, therefore, be used for stimulation.) The effects upon the *skeletal and cardiac muscles* are qualitatively identical with all the members.

With reference to their action, a series may be formed running: Sarcin, caffein, theobromin, and xanthin, the former with the maximum stimulating effect upon the central nervous system and with the least rigor effect upon the muscles; the latter with the greatest action on the muscles and with the maximal paralyzing effect upon the central nervous system.

With regard to the *diuretic action*, the various di-methyl-xanthins are the strongest.

Of these, theobromin, although the most extensively used, and greatly superior to caffein, is still the weakest, paraxanthin and theophyllin being much stronger. Xanthin has only a very weak diuretic action.

Uric Acid shows itself absolutely inactive. The painful inflammation which it causes when introduced into joints in the solid form (through ligation of the ureters or injection into birds, or spontaneously in gout) is purely mechanical. It would seem, however, that the presence of a large amount of uric acid causes a tissue-necrosis, and that this furnishes the condition for its crystallization.

The action of the other members of the series, the meat bases, and especially creatin and creatinin, upon muscle deserves much more thorough investigation than it has thus far received. Large doses of creatin and creatinin cause headache, nervousness, and slowing of the heart.

VI. TOXICOLOGY.

The toxicology of caffein is unimportant. The *symptoms* produced by large, but not fatal, doses have been sufficiently discussed; those arising from the *central nervous system* are: excitement, increased reflex irritability, tremors, etc. These predominate, and are associated with *palpitation* and quickened, irregular pulse.

Fatal doses—very rare in man—show tetanus, coma, and death, usually by paralysis of the heart. There are no postmortem lesions.

The *treatment* would consist in evacuation, and bromids or other narcotics. The usual chemic antidotes are of little value, with the exception of permanganate.

VII. THERAPEUTICS.

(*A*) *The Effects upon the Spinal Centers.*—These are not much utilized, since the same effects are obtained by strychnin in a better and purer form. Strychnin avoids especially the action upon the brain (wakefulness) and heart (palpitation).

(*B*) *The Effect upon the Medullary Centers.*—Here, also, strychnin is preferred in almost all cases where it is at hand, for doses of caffein large enough to affect the medulla are apt to have the above side-effects.

In cases of *narcotic poisoning*, where strychnin is often not at hand, and especially in morphin and alcohol poisoning, where it is wished to stimulate the brain as well, this drug is very useful. Caffein forms a useful addition to drugs, such as the *antipyrin* series, in which depression of the central nervous system is an undesired side-action.

It may also be of great service in certain cases of *asthma*.

The use of caffein in *migraine* is entirely empirical, since the nature of this disease is not known. It is undoubtedly useful, especially in the combination known as migrainin.[1] It is also used in trigeminal neuralgia, and often gives relief. It is possible that these actions are due to the effect on the higher centers. Caffein may be similarly useful in *nervous dyspepsias*.

(*C*) *Its effects on the brain* are the most important, but can be better discussed under its habitual use.

(*D*) *Effect upon the Kidneys.*—On account of the antagonism in the action on the vasomotor center and renal epithelium, the effect upon the urine is somewhat variable. As has been said, the smallest effective dose should be used, preferably combined with chloral or paraldehyd. Theobromin or diuretin (theobromin-sodium salicylate) is much superior to caffein. The use of these drugs would be especially *indicated* when there is a diminution of the urine without inflammation of the kidney; *e. g.*, in ascites from heart disease. It would in this case be usefully joined with digitalis.

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[1] Caffein, 9; antipyrin, 85; citric acid, 6. Used in doses of about 0.6 Gm. (10 grains).

(*E*) *Effect upon the Heart.*—Caffein has been used considerably in heart disease, especially in stenosis and mitral insufficiency. Neither clinical observation nor pharmacologic experiments have assigned to it so prominent a place as to digitalis, and it may well be discontinued for this purpose.

VIII. CAFFEIN BEVERAGES.[1]

Before proceeding to the study of the habitual use of caffein, it will be well to consider the *effects of other constituents* found in these beverages. The principal of these is *tannin*. This is extracted rather slowly by water, and will, therefore, be found in the greatest amount when the boiling has been prolonged for some time. It is mainly responsible for the bitter taste. It interferes with digestion and absorption. It is the tannin, contained especially in strong tea, which causes this to be used as an antidote in alkaloidal poisoning.

Besides tannin, coffee contains *empyreumatic products* (caffeol) developed during the roasting. These have a stimulating effect upon the central nervous system, both direct and reflex, but no action upon muscles. They determine the difference in the action of unroasted and roasted coffee. A similar action exists in the case of tea, through the presence of *essential oils*, especially in the green teas, the same differences existing between green and black tea as between roasted and unroasted coffee.

The caffein-free distillate from infusions of tea or roasted coffee causes an increase in rate of respiration, and a psychic and muscular restlessness. The pulse is not altered.

The principal benefit derived from these beverages is a *diminution of fatigue*, mental and muscular. The action on *mental fatigue* is accounted for by the stimulation of the psychic areas, an action greatly enhanced by the volatile by-products. For this purpose one should, therefore, employ well-roasted coffee or green tea with short infusion. These would also be especially active in producing wakefulness.

The effect upon the *muscular fatigue* may be explained both by easier transmission of reflexes (a given stimulus reaching the muscle more readily) and by increased contractility and excitability of the muscle-fibers themselves.

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[1] The use of coffee arose in Arabia and Egypt about 1450. Coffee and tea were introduced into Europe about the last quarter of the seventeenth century, a period which was characterized by the common introduction of many new products, such as the potato, cinchona, tobacco, and chocolate.

This action has been demonstrated beyond a doubt; *e. g.*, soldiers can endure more severe marches when given coffee. It can also be demonstrated with the ergograph. It will occur only if the amount of energy-yielding substance in the muscle has not been exhausted, and will not have any effect after fasting. Sugar is then the most efficient means for the relief of fatigue.

The action does not seem to be followed by any extra depression. Since it is caused by the caffein itself, it can be secured most easily by unroasted coffee or black tea. In all these cases the reflex stimulating effect of the hot water undoubtedly plays a rôle.

Coffee is sometimes used against *hunger*. It acts only by covering up the condition through the exhilaration which it produces, and cannot be of any real benefit. On the contrary, the metabolism is increased.

The *habitual use of caffein beverages* depends upon the pleasant sensations which accompany the stimulation. Caffein *in moderate doses does not seem to become noxious with habitual use*. When the amount taken is too large, it presents the same symptoms in persistent form which are seen in acute poisoning: tremors, nervousness, palpitation, etc. The mind also seems to suffer, and *chronic melancholia* is a frequent phenomenon.

The *effects of the continued action of the tannin* are perhaps even more deleterious than those of the caffein. They may cause very serious *interference with digestion*, and produce a tendency to *constipation*. Small amounts of coffee seem to have a somewhat *laxative action*. The tannin is, of course, most injurious when the amount of the beverage consumed is excessive. Tea is therefore generally the more injurious in dyspepsia, yet sometimes coffee does more harm through its nervous action.

Cocoa and chocolate are also used as mild stimulants, their effects being less pronounced than with the others. On account of the large amount of fatty matter which they contain, they are to some extent nutritious, although this fat is not very digestible.

These beverages are also used to cover up the taste of medicines; *e. g.*, iron, quinin, bitter substances, castor oil, cod-liver oil, etc.

IX. BEEF-TEAS AND SIMILAR PREPARATIONS.

The therapeutic effects of beef-teas, soups, meat-extracts, etc., may be considered in this place. It is scarcely necessary to mention that these have practically *no nutritive* *value.* Their effects are only those of *stimulants*, being due to the leucomain-substances of the meat; *i. e.*, substances belonging to the caffein series and acting mostly upon the central nervous system and muscle. Here belong: xanthin, hypoxanthin, carnin, sarcin, creatin and creatinin, and others. All these leave the body practically unchanged; *i. e.*, do not yield energy and are not therefore food.

These **leucomains** result largely from the decomposition of nucleins. Three classes may be made out:

1. Xanthic; precipitated by heat in acid solution in the presence of copper acetate; also by silver nitrate.
2. Creatinic; not precipitated by the above, but by $ZnCl_2$ or $CdCl_2$.
3. Neurinic; not precipitated by any of the above.

Although the main stimulating action of these preparations must be attributed to these leucomains, there is, in addition, an auxiliary action of volatile products, just as in coffee and tea.[1]

These furnish the explanation of all the observed effects. Even the theory that bouillon increases the digestibility of vegetable proteids has been proved erroneous.

In addition to the above, beef-tea and soups favor, through dilution, the absorption of substances which do not need digestion. They also favor the secretion of gastric juice, and this action probably outlasts the dilution. Soups do have a certain amount of nutritive value on account of their gelatin. This, though not capable of being utilized for the construction of tissue, is capable of largely replacing it in metabolism, and thus the effect is the same.

If it is really desired *to nourish the patient with nitrogen*, one must have recourse to other means. The usual object is to introduce a fair amount of nitrogenous food with the minimum tax on the digestive organs. This may often be done by proper selection of the diet. When this does not suffice, one should have recourse to partly predigested foods. (See also Chap. XXXII.)

1. *Beef juices:* tissue fluid, expressed from meat without heat. Their advantage lies simply in the mechanical removal of the fibers. They contain 6% to 12% of coagulable proteid, and theoretically at least, it is difficult to see in what way they would be superior to raw eggs mixed with beef-tea, which would be very much cheaper. Perhaps they are more digestible.
2. *Beef-tea made with dilute HCl* (0.2% to 0.4%) instead of water. It

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[1] The potassium salts have also been invoked to explain the action, it being claimed that they stimulate the heart in moderate doses and paralyze it in large doses. But the dose required to produce the former effect is very much larger than would be administered in beef-tea.

would seem on theoretic grounds that this could be made quite nutritious, although there are few clinical data. Alkali albuminates derange the stomach.

3. *Commercial peptone, peptonized milk,* etc. Very concentrated preparations of peptones have a disagreeable taste, especially if the digestion has not been thoroughly aseptic. The taste, however, can be disguised by artificial means. It has been shown, both on man and dogs, that all the nitrogen required by the body may be given as "peptones"—*i. e.*, albumoses—without deranging the digestion, but it has not yet been experimentally demonstrated that this is any better than meat.

The *liquid preparations of peptone* found on the market usually contain less than 0.5 % of nitrogen; less, therefore, than milk, and only about three times as much as beef-tea. To get the minimum of nitrogen required (13 Gm.) would take three liters of such preparations, whereas they are given in doses of, at most, 100 c.c. per diem. The benefit derived from them must be attributed particularly to the alcohol or other stimulating substances contained therein.

Bouillon.—One kilo of medium lean beef gives 2.5 L. bouillon of the following composition (Gautier):

	Per Liter.		
Albuminoids	7.5	Gelatin	1.72
		Albumose	0.48
		Peptone	5.30
Creatin Bases	0.9		
Xanthin	0.25		
Taurin, etc.	0.12		
Inosite and Glycogen	1.40		
Lactic acid	0.20		
Extractives	4.60		
Soluble mineral salts	3.76	$FeHPO_4$	0.02
Insoluble mineral salts	0.38	$CaHPO_4$	0.12
		HCl	0.72
		$NaCl$	0.15
		K_2SO_4	0.35
		K_2HPO_4	2.60
		$MgHPO_4$	0.23
	19.11		

X. TOXIC ACTION OF URINE.

The same extractives or leucomains which are contained in meat-extracts or muscle are also found in urine. The toxic action which urine possesses when injected intravenously has been variously attributed to these leucomains, to toxins, etc., and at one time even to the urea. Various brilliant theories and methods of diagnosis were built upon the variations in this toxicity. It has, however, been shown that about 85 % of the toxicity of the urine is due simply to its potassium salts. The symptoms are also precisely those of the latter. What causes the other 15 % of the toxicity is at the present not known, but this may be connected with xanthin products. Since the quantity of the latter is determined quite as much by the xanthin-bodies taken by the food as by those formed in the body, this does not make the method any more valuable. The above refers, of course, only to normal urine. It is possible, and indeed likely, that poisons are excreted through it in disease, but one cannot sufficiently oversee the factors at the present time to utilize them.

MATERIA MEDICA.

⁂ **Caffea.**—*Coffee.*—Seed of *Coffea Arabica*, Rubiaceæ.[1] Native of Arabia and Abyssinia, cultivated in all tropical countries.

Caffein, 1 to 1.3% ; tannin.

The leaves also contain caffein, and are used by the natives in the same manner as tea.

In the process of roasting, a very small amount of caffein is lost (depending upon the degree of heat used), and empyreumatic oils ("caffeon"), of unknown composition, are produced.

An ordinary cup of coffee contains 0.1 to 0.2 Gm. of caffein.

Preparations :

* *Fluid extract of green or roasted*, N.F.

⁂ *Syrupus Caffeæ*, N.F.

⁂ **Thea.**—*Tea.*—Leaves of *Camellia Thea*, Ternstrœmiaceæ. Southeastern Asia, cultivated. (Also capable of cultivation in the United States.)

Caffein, 1.5 to 4% ; volatile oil ; tannin, 11 to 24%.

An ordinary cup of tea contains 0.1 to 0.2 Gm. caffein.

The black and green teas differ only in the treatment to which the leaves are subjected (a fermentation with the black variety).

* *Extractum T. fluidum*, N.F.

* **Kola.**—*Cola.*—Seed of *Cola acuminata*, Sterculiaceæ. Tropical western Africa and cultivated in West Indies.

Caffein, 2% ; a little theobromin formed from glucosid in drying ; volatile oil ; tannin.

Often roasted. Used by the natives as masticatory and to render bad water palatable. Valued so highly as to be used as money.

* *Fluid Extract*, N.F.

Guarana.—*Guarana* (Brazilian Cocoa).—A dried paste, prepared by the Indians, consisting chiefly of the roasted and pounded seeds of *Paullinia cupana*, Sapindaceæ, northern and western Brazil.

Caffein, 4 to 5% ; tannin, gums, resin, volatile oil.

Extractum Guaranæ Fluidum.—Alcohol, three-fourths. Miscible with water and alcohol. *Dose :* 1 to 4 c.c. (¼ to 1 drachm).

* **Maté.**—*Paraguay Tea.*—The leaves of *Ilex paraguayensis*, Ilicineæ. Brazil and Argentine.

The commercial leaves are slightly torrefied.

Caffein, 0.2 to 1.6% ; tannin, 10 to 16% ; little volatile oil.

Used in making a beverage.

Other species of Ilex probably also contain caffein, and some of those growing in the Southern States are used as *Apache tea.*

Theobroma.—*Cacao* (not to be confused with Coca !).—The fermented, dried, and often roasted, seeds of *Theobroma Cacao*, Sterculiaceæ. Tropical America, cultivated.

Theobromin, 1.5 to 4.5% ; trace caffein ; fat, 50% ; starch, 10% ; tannin.

The theobromin does not exist in the fresh seed, but is derived from a glucosid during the process of preparation. In the powdered cacaos of commerce, part of the oil has been removed, so that only about 25% remains.

Chocolate consists of melted cacao and sugar in various proportions, often with the addition of flavors or starch.

Caffeina, U.S.P., B.P.—Tri-methyl-xanthin, prepared from any of the above plants. The free base is soluble in 80 water; 33 alcohol. *Dose:* 0.15 to 0.5 Gm. (2 to 8 grs.).

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[1] The same order yields cinchona, catechu, and ipecac.

Triple asterisk = most important preparations.

Single asterisk = not official.

U.S.P. = official in United States—B.P., in British Pharmacopœia ; N.F. = National Formulary.

Preparations:

⁂ *C. Citrata*, U.S.P. (Caffeinæ Citras, B.P.) (not a true salt, but a mixture).—Soluble in 3 water. *Dose:* 0.15 to 0.5 Gm. (2 to 8 grs.).

⁂ *C. Citrata Effervescens*, U.S.P., B.P. = 10% of caffein. *Dose:* 4 to 15 Gm. (1 to 4 drachms).

* *C. Sodio-bensoas*, N.F.
* *C. Sodio-salicylas*, N.F. } = 50% caffein; soluble in 2 parts water.

⁂ *Elixir Caffeinæ*, N.F.—1.75%. 4 c.c. (1 drachm) = 0.06 Gm. caffein (acidulated).

⁂ Theobrominæ *sodio-salicylas* (*Diuretin*) = 50% of theobromin. Soluble in ½ part water. *Dose:* 1.5 to 3 Gm. (20 to 45 grs.).

(This preparation should be kept air-tight, since CO_2 renders it insoluble in time.)

BEEF PREPARATIONS.

* *Extractum Carnis Liebig.*—Beef-extract.—An evaporated decoction of meat.

Composition of Liebig's Extract.

	PER CENT. (GAUTIER.)	
Water	15.26	
Coagulable proteids	0.05	Albuminoids 36.93
Gelatin	8.49	
Albumose	2.32	
Peptone	26.07	
Creatin bases	8.30	
Xanthin bases	0.89	
Inosite and glycogen	2.20 to 4.25	
Extractive matter	11.98	
Soluble mineral salts	21.26	
Insoluble mineral salts	1.13	

Any other similar preparation of meat-extract may be used instead.

* *Vinum Carnis*, N. F.—*Wine of Beef:* 3.5% Liebig's extract in sherry wine.

⁂ *Vinum Carnis et Ferri*, N. F.—*Beef, Iron, and Wine:* The preceding with ⅓% of iron chlorid.

* *Vinum Carnis, Ferri et Cinchonæ*, N. F., contains, in addition, 0.3% cinchona alkaloids.

(C) PICROTOXIN GROUP.

This comprises a number of bodies closely related by their pharmacologic action, and probably also by their chemic composition. Of the latter little is known. They belong to a group of non-alkaloidal, non-nitrogenous vegetable substances, more soluble in alcohol than in water, sometimes called "active resinoids" Some of them are glucosids. The group has at present very little therapeutic but some toxicologic interest.

Triple asterisk = most important preparations.
Single asterisk = not official.
U.S.P. = official in United States—B.P., in British Pharmacopœia; N.F. = National Formulary.

I. MEMBERS.

Picrotoxin, from Cocculus indicus.
    Splits easily into Picrotoxinin—same action.
                                Picrotin —harmless.
Cicutoxin, from Cicuta virosa—water hemlock.
Œnanthotoxin, from Œnanthe crocata.
Coriamyrtin, from Coriaria myrtifolia.
Digitaliresin—decomposition product of digitalin and digitalein.
Toxiresin—decomposition product of digitoxin.
Oleandresin—decomposition product of oleandin.
Phytolaccotoxin, mainly from Phytolacca Japonica, but probably also in Ph. decandra.

II. SUMMARY OF ACTIONS.

1. Stimulation, followed by paralysis, of the medullary centers.
2. Some stimulation of the spinal cord.

III. DETAILS OF ACTION.

The effect upon the *medulla:* The principal symptom from picrotoxin poison consists in *convulsions* of the same character as those described on page 158 as characteristic of a stimulation of the medulla. They are, indeed, situated in the medullary convulsion-center, since they are not affected by excision of the cerebrum, but practically disappear after destruction of the medulla.

This is especially the case in mammals. In the frog, strychnin-like spasms of spinal origin often appear shortly after the medulla is destroyed, which were before masked by the more intense stimulation of higher centers.

The convulsions are not so much dependent upon reflex stimulation, so that they are probably in part due to a direct stimulation.

Respiratory center: The respiration is accelerated before the convulsions. Later it becomes fixed in the spasm, and in the following collapse may be slowed. Asphyxia may, therefore, occur.

Spasms of the laryngeal muscles leads, with the frog, to distention of the body with air and to a characteristic cry similar to that sometimes heard with strychnin. With digitaliresin, toxiresin, and oleandresin, the convulsions are preceded by immobility.

Vasomotor center: There is a general rise of blood pressure, notwithstanding the slowed pulse, and independent of the convulsions, showing a stimulation of the center.

Vagus center: The heart is greatly slowed, and may even cease for a time. After division of the vagi the heart will return almost to normal. There is, however, some depression of the cardiac muscle involved in this slowing. Later there may be a quickening, partly due to stimulation of the accelerator center and partly to paralysis of the vagus center and to fatigue of its endings.

The *vomiting*, *salivary*, and *sweating centers* are also excited. The sweat may, however, be suppressed by vasomotor constriction. The emetic effect is used therapeutically in the case of phytolacca.

Spinal cord: As has been seen, a stimulation of this structure is shown, under suitable conditions, by increased reflex irritability. The centers of defecation and urination may also be excited. Uterine spasms have also been observed as dependent on stimulation of the cord, since they cease upon destruction of this organ.

With larger doses, all the stimulant effects give way to paralysis.

IV. TOXICOLOGY.

Poisoning with the common plant Phytolacca (poke-berries) is not rare. The Cocculus indicus (fish-berries) have been used for poisoning fish (in whom it also produces medullary stimulation and paralysis), and this meat is highly toxic. It has also been used to give a bitter taste to beer, which thus becomes poisonous. 2.4 Gm. of the berries (0.015 to 0.025 Gm. of picrotoxin) are fatal. The toxic effect sometimes seen on administering old infusions of digitalis may also be due to members of this series. More direct work on this would be desirable.

The *symptoms* of poisoning consist in: vomiting, salivation, acceleration of respiration, slowing of pulse and palpitation of heart; stupor and unconsciousness; tonic spasms passing into clonic; collapse; repetition of spasms; asphyxia.

The best proof of the poison would be the physiologic effects, the characteristic action on the frog, producing bucking and bloating.

Treatment.—The chemic alkaloidal precipitants would, of course, not be efficient. The best treatment would be emetics (if vomiting has not occurred), chloral, and chloroform. The combined administration of chloral, morphin, and minimal doses of atropin has recently been recommended as the result of animal experiments.

V. THERAPEUTICS.

The medullary stimulation produced by this group would be highly important if we could find members which were quickly and certainly absorbed. This has not been accomplished so far, the action being uncertain and difficult to control. Coriamyrtin holds forth some promise, but has not been sufficiently tried. The indications for their use would be the same as those for strychnin (medullary effect). Phytolacca has been used as an emetic, but its action is uncertain and is apt to be followed by dangerous effects. Picrotoxin is used externally against pediculi; internally, against the night-sweats of phthisis, and in epilepsy, where its benefits are, however, doubtful.

MATERIA MEDICA.

* **Cocculus indicus.**—*Fish-berries.*—The seeds of *Anamirta paniculata*, Menispermaceæ. East India.

Picrotoxin, alkaloid, resin, fat, anamirtin.

Dose: 0.1 to 0.2 Gm. ($1\frac{1}{2}$ to 3 grs.).

(Decoction used externally for killing vermin.)

Picrotoxinum (U.S.P., B.P.).—*Picrotoxin.*—Neutral principle.

Soluble in 9 alcohol, 240 water.

Dose: 0.0005 to 0.002 Gm. ($\frac{1}{120}$ to $\frac{1}{30}$ grain).

Action uncertain.

* **Cicuta virosa.**—*Water Hemlock.* Europe.

Cicuta maculata and bulbifera. United States.

Umbelliferæ. Of some toxicologic interest.

Phytolaccæ Fructus (U.S.P.).—*Poke-berry.*—The fruit of *Phytolacca decandra*, Phytolaccaceæ. North America.

Phytolaccotoxin, gum, coloring-matter.

Preparations:

Extractum Phytolaccæ Fructus Fluidum (U.S.P.): Two-thirds alcohol. *Dose:* 0.3 to 2 c.c. (5 to 30 minims).

* *Succus Phytolacca Fructus:* The fresh juice. *Dose:* 2 to 4 c.c.

Phytolaccæ Radix (U.S.P).—The root of the above.

Constituents as above; also tannin and oils.

Dose: 0.3 to 2 Gm. (5 to 30 grains).

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* Not official.

(Poke-root and berries are used popularly as emetics, cathartics, and "alteratives.")

(D) SUMMARIES OF CONVULSANT SERIES.

1. Drugs Stimulating the Vasomotor Center.—*A rise of blood pressure may be brought about* by a quickening of the heart, by an increase of the volume of blood thrown out at each contraction, or by a *contraction of the vessels.*

The latter may be effected *peripherally*, either through direct action on the muscles or the endings, or it may be effected through the vasomotor *center.*

The vasomotor center may be stimulated:

1. Reflexly, through stimulation of the sensory nerves.
2. Directly, through accumulation of CO_2 in the blood.
3. *Directly, through the action of drugs.*

The latter alone will be considered in this place. The following drugs stimulate the vasomotor center directly:

Strychnin: the action is rapid and free from side-effects.

Caffein: large doses are required and such as will produce headache, wakefulness, and perhaps palpitation.

Picrotoxin Group: the action of this is confined to the medulla, and would for that reason be the most desirable; however, the action develops slowly and is difficult to control.

Digitalis Group: the vasomotor action is overshadowed by a simultaneous stimulation of the cardiac muscle, which is, however, usually desirable. The effect is developed rather slowly—in half an hour.

Groups of Atropin, Aconite, Nicotin, Ergot, and Ammonia: the effect is small, uncertain, and obscured by side-actions.

A stimulation of the vasomotor center will be *useful* by producing a rise of the blood pressure. The benefit will only be *temporary if the low pressure is due to cardiac failure*, since the rise is produced at the expense of the heart; *i. e.*, by increasing its work. The benefit is *more permanent when the center is depressed*, as in shock, narcotics, or in partial paralysis of the center.

The direct stimulation of the center by drugs (strychnin) has the *advantage over reflex stimulation* in that it can be maintained continuously for a much longer time. Reflex stimulation is more useful when a short but quick stimulation is desired.

2. **Respiratory Stimulants:** *i. e.*, those conditions which quicken or deepen the respiration through a stimulation of the respiratory center.

This stimulation may be:

1. Reflex, from stimulation of peripheral nerves.
2. Direct, through an increase in temperature or venosity of the blood.
3. Direct, through drugs.

Drugs stimulating the respiratory center directly:

Strychnin has a quick and powerful action, practically free from undesired side-effects, but the effect is *not lasting.*

Caffein acts more slowly, but is more lasting; it produces wakefulness, etc.

Atropin: the effect is not so very great, but since it also paralyzes the bronchial muscles and dries the bronchial secretion, it is especially indicated in *asthmatic conditions.*

With the groups of *picrotoxin, HCN, and* NH_3, the action is uncertain and impure.

Indication for these remedies is lowered activity of the respiratory center, such as may occur in exhausting diseases; fatigue, as in asthma; or in depression by drugs (narcotics).

3. **Convulsants.**—As far as these have toxicologic importance:

Convulsions may be produced by asphyxia or through direct stimulation of the convulsion centers.

Asphyxial convulsions can be removed by artificial respiration. They occur in the course of poisoning by many drugs which depress the respiratory center or interfere mechanically with the admission of air into the alveoli. To the former belong chloroform and anesthetics; to the latter, CO, CO_2, and N_2O_2.

Drugs may stimulate the center either in:

Motor areas, Pons, Medulla.	The convulsions are epileptiform or choreiform; if tonic, there is emprosthotonos.
Spinal cord:	The convulsions are tetanic; opisthotonos.

Usually the seat of the convulsion is more or less widely spread, and there is perhaps no drug which affects exclusively one of these centers.

Spinal convulsions exist most typically with:

Strychnin group.
Caffein "

Medullary convulsions:

Picrotoxin group, including digitalis.

Cornutin.
Camphor.
Ammonia.
Veratrin.

Typical *cerebral convulsions* are seen with:

Cannabis indica.
Absinthe.

4. Shock or Collapse.—Shock or collapse may be defined as a sudden depression of the activity of the medullary center. If this depression results from a reflex, it is called shock; if produced directly, collapse.

Collapse may be produced by anemia, asphyxia, or drugs.

In any case there is an involvement of the vasomotor and respiratory centers, also of the cardiac (vagus center); but the latter is of very little practical importance.

Depression of the heart may be the cause of the anemia.

Drugs causing collapse:

I. Indirectly:

1. All which stop the heart.
2. All those which interfere mechanically with respiration.
3. Those which produce a violent reflex irritation (caustics).

II. Directly: i. e., those in which the collapse is not preceded by other conspicuous symptoms:

Cocain.
Physostigmin.
Benzol derivatives (aromatic series).
Hydrocarbon narcotics.

Treatment of Collapse.—If the collapse is indirect, the treatment should be the *removal of the cause;* if direct and if the *respiration is paralyzed*, artificial respiration or heat should be used.

If the *vasomotor paralysis* is most conspicuous, one may use strychnin, usually joined with *hypodermic injection of normal salt solution* (50 c.c. at frequent intervals to 300 or 1000 c.c.). The normal salt solution has a very marked influence on these conditions. It slows and strengthens the heart-beat and brings about a rise of both arterial and venous pressure. It has not nearly as strong an effect when the circulation is normal, and the action is in all cases only short; the injection must therefore be repeated. The quantity necessary to produce a marked change is of such an amount as to favor the idea that it acts largely mechanically—*i. e.*, by increasing the fluid in the circulation; but it seems also to produce a stimulating action on the medullary centers, perhaps due to reflexes set up in the blood-vessels on account of the mechanical salt irritation. It is most efficient at a temperature of 50° C., but is then painful. In case of emergency it may be injected into the peritoneum or intravenously.

These measures are more useful in shock or collapse than stimulation of the medullary center through reflex irritation, for when the vasomotor center is depressed, reflex irritation is apt to have a rather depressant action upon it.

The application of heat and lowering of the head are always useful in conjunction with other treatment.

CHAPTER IX.

ALKALOIDAL HYPNOTICS.

(A) MORPHIN GROUP.

I. MEMBERS.

THE members are mainly the various opium alkaloids: Morphin, codein, narcotin, papaverin; also the substitution products obtained by replacing one or more H of morphin by a hydrocarbon radical:

Heroin = di-acetyl-morphin.
Dionin = acetyl-morphin.
Peronin = benzyl-morphin.

These are formed on the type of codein, which is methylmorphin.

II. SUMMARY OF ACTIONS.

1. Simultaneous stimulation and depression of different parts of the central nervous system.

2. A local action on the peristaltic mechanism of the intestine.

3. An HCN action on the heart.

(There is no effect upon the peripheral sensory nerves.)

III. DETAILS OF ACTION.

1. Central Nervous System.—(A) The Brain.—(*a*) In the *frog* the development of the symptoms corresponds exactly to progressive removal of the brain. They can be well made out if the poisoning is slow. The depression begins with the *hemispheres*. There is a diminution, and then absence, of spontaneous movements; but when aroused, the animal will act quite normally. It sits in the normal position, shows the croaking reflex, and will climb up an inclined plane. When placed in a tumbler filled with water and inverted in a large vessel of water, it will at first leave the glass, but later on it will not do so. At this time it will not avoid obstacles in jumping. The lower brain is next involved, this being shown in an *incoordination* of movements. When placed on its back, the animal will make efforts to turn, without being able to do so. Later it will lie quiet. The *spinal cord* is then involved and the reflexes are lessened.

After the animal has remained in this depressed condition for a variable time a *secondary tetanus* sets in. This is of the strychnin type. It usually passes into complete *paralysis*. The heart is still beating at this stage.

Why this tetanus does not appear at once is still problematic. One would be tempted to suppose that it is masked in its early stages by the depressing action of the poison, but this is rendered improbable by the fact that it appears early if large doses are given. It may perhaps be assumed that the narcotic action soon reaches the maximum, whereas the stimulating action still increases.

Another theory would be that a tetanizing substance is gradually developed by the morphin. The subject needs investigation.

Heroin also produces this secondary tetanus.

(*b*) In *mammals* the course is similar, although there is not such an isolation of the symptoms, both because the centers are more intimately correlated and because the action is more rapid. The secondary tetanus is less prominent, but in small animals quite manifest. A stimulation of various parts of the central nervous system, simultaneous with the depression of others, is much more conspicuous than in the frog.

One or the other of these two sets of actions, stimulation or depression, may predominate in different animals or in different individuals of the same species. On account of these individual differences, the symptoms are not uniform, and it is impossible to pronounce on one type of morphin-poisoning. Each part of the central nervous system requires separate study.

Hemispheres.—In mammals the *first effect*, produced by doses too small to elicit any other symptoms, is *diminished sensibility to lasting impressions.* Especially stimuli giving rise to *pain, cough*, and other disagreeable sensations, are much diminished in their effects. With somewhat larger doses other persistent external impressions, such as those produced by light, sound, etc., are also weakened. The *sensibility to sudden stimuli is diminished but not abolished.* It seems to be the *attention* which suffers mainly. The impressions reach the brain, but produce little effect there, and, attracting little attention on the part of the animal, are neglected. These conditions exist in practically all animals possessed of a higher brain.

In *larger doses* morphin affects other portions of the hemispheres besides those having to do with external impressions, and the effects upon these are variable. Its typical effect in man is to produce *quietness*, which, aided by suppression of external stimuli, passes into a dreamy, abstracted condition, or into torpor, *sleep*, and coma, according to the dose. Since the patient can be completely awakened, at least in the earlier stages, and since the sleep produced by small doses is refreshing, this goes, with other facts, to show that the early paralysis does not involve the whole brain, but is largely the effect of the exclusion of stimuli.

But the morphin may have precisely the opposite effect. Thus, in the cat tribe it produces almost pure *excitement*, manifested by restlessness and incessant movement.

But even in this condition one may notice the depressing action upon the attention, for the animal does not avoid obstacles in a normal manner, and when it comes into violent contact with some object, this does not seem to make any lasting impression upon it, and does not teach it to be more careful.

Some Eastern races, especially the Malays, as well as some individuals of other races, most frequently women, also manifest almost pure excitement effects, so that the morphin produces wakefulness instead of drowsiness. In many cases this restlessness seems to precede the narcotic action,[1] although not the lowering of the attention.

The *other members of the group*, especially codein and heroin, show a comparatively slight quieting, and comparatively strong excitant, action. With these, the maximum of hypnosis is soon reached, and if the dose be raised beyond this point, the slight depressant action disappears entirely and is replaced by excitement. These phenomena seem analogous to the secondary tetanus. Different animals show the same differences with regard to the narcotic and stimulating actions of these derivatives as they do with morphin.

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[1] *Narcotics* are substances having the property of stupefying. The following drugs are classed under this heading: Aconite, hydrocarbons, belladonna, cannabis, conium, digitalis, humulus, hyoscyamus, lactucarium, opium, and stramonium.

Morphin is by far the most active member of this series, as far as the hypnotic and analgesic effects are concerned. Whether these successive stimulations and depressions involve the same or different centers cannot be decided. Either view has some support.

The *motor areas* may be very differently affected. In dogs one sees very frequently a paralysis of the hind legs, resulting in a crouching (hyenoid) walk, which probably has its cause in depression of this center. They always show a clumsiness in their voluntary movements, bearing the closest resemblance to that produced by ablation of the motor areas. Heroin gives the same effects.

On the other hand, one often sees epileptiform convulsions, tremors, or choreiform twitchings of single limbs which seem to arise from irritation of this center. The excitability of the motor areas to electric stimulation is not affected.

On the *special senses* morphin seems to have no effect. The changes which are noted—namely, a less acute perception—can be accounted for entirely by disturbance in the attention.

On the other hand, the reflexes to which they give rise when suddenly excited, are increased. This depends upon the *heightened excitability of the spinal cord.*

The *imagination* is peculiarly affected. In most people the period of abstraction and light sleep is filled with dreams which are usually pleasant.

At least the greater part of this may be ascribed to the suppression of the external, and especially of unpleasant, impressions. Whether there is also a stimulation of an "imagination center" must be left undecided. Perhaps the *aphrodisiac effects* can be explained by this unrestrained imagination, perhaps also by stimulation of the center in the cord, for the more stimulating members of the group, such as heroin, always produce erection in dogs.

(B) **The Medulla.**—The effects upon the medulla are very characteristic. There is less variation in individuals, but the separate centers show a very different reaction.

(*a*) *The Respiratory Center.*—The respiration is slowed, and the excitability of the respiratory center to reflex stimulation is greatly lessened. The excitability to CO_2 or to the absence of oxygen is not so much diminished, at least with heroin. The individual respirations become deeper, the inspiration relatively prolonged, and the force increased. The oxygen consumption is, of course, lessened by this action, except with the more convulsive member of the group (codein). With heroin, the blood is but little, if any, richer in CO_2. With this drug (heroin) the effect upon the respiratory center is so marked that the dose may be adjusted in such a manner that this will be its only action.

A comparison of the action of different members of this group will be of interest (doses given are per kilogram of rabbit):

	HEROIN.	MORPHIN.	PERONIN.	DIONIN.	CODEIN.
Doses giving maximum therapeutic effects	0.5 mg.	2.5 mg.	15.0mg.	6.0 mg.	10.0mg.
Fatal dose equals times therapeutic dose	200.0	80.0		16.6	10.0
Velocity of action	7 minutes.	9 minutes.	14 minutes.	10 minutes.	10 minutes.
Mean decrease in frequency, per cent.	52	35	14	20	28
Mean decrease in volume respired in given time, per cent.	38	34	16	19	23
Mean increase in volume of single respiration, per cent.	39	12	13	5	18
Comparative dose . . .	1	5.0	30	12	20
Comparative danger . .	1	2.5		12	20
Effect on volume of individual respirations, per cent. . .	7.8	2.2	2.5	10.0	3.6
Effect on frequency, per cent. .	3.7	2.5	1.0	1.4	2.0

Other investigators claim that the difference between the therapeutic dose of heroin and that producing unpleasant side-effects is not so very large. The bulk of evidence certainly inclines to the view that it is a comparatively harmless depressant of the respiratory center to reflex stimulation.

With *larger doses* of morphin the respiration becomes more shallow and more irregular, frequently of Cheyne-Stokes type.[1]

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[1] Cheyne-Stokes respiration is seen with a very large number of drugs which have in common a depression of the respiratory center. It is now believed to be due to the effects of change of blood pressure on the respiration when the activity of the respiratory centers is lowered. These changes in respiration depend on the Traube-Hering curves in the blood pressure, and these, in turn, appear whenever the respiratory center is greatly depressed. They arise through a rhythmic stimulation of the vasomotor center, and a periodic rise of pressure produced in this manner reacts upon the activity of the respiratory center in its depressed condition.

The weakened respiration results, with morphin, in a great accumulation of CO_2 in the blood—more even than in chloroform-poisoning. This leads to asphyxial convulsions, and these, added to the increased muscular activity produced by the spinal action of the drug, lead to a greater need of oxygen. This the weakened respiration cannot supply, and the animal, therefore, dies. It will be seen from this that those members of the morphin group are most fatal which produce at once a depression of the respiratory center and convulsions. Paralysis of this center is usually the cause of death. The asphyxia has the usual effects, already described on page 162.

(*b*) *Effects on the Circulation.*—Morphin has very little action except in maximal doses. The rate of the heart is at first slightly accelerated, then slowed, the former being secondary to the nausea. Larger doses cause slowing through *stimulation of the vagus center.*

That the slowing in this stage is due to the stimulating action is shown by the fact that it can be partly removed by anesthetics.

Somewhat larger doses will, of course, depress this center. Maximal doses may also paralyze the *automatic motor property of the heart* in the same way as HCN; *i. e.*, the rhythmic contraction will have ceased when the heart muscle is still capable of responding to stimulation by isolated contractions. Still larger doses abolish the contractility altogether. Heroin has practically the same action on the circulation, but a stronger effect on the vagus center.

The *vasomotor center*, as a rule, is not affected except in the highest grades of poisoning, when it is depressed with little, if any, previous stimulation. With moderately large doses the *blood pressure* is not changed. If the asphyxia is pronounced, one may observe the asphyxial rise and fall. There is a somewhat specific stimulation of the vasodilator center for the *cutaneous vessels* even with small doses. The skin becomes red. There is a feeling of warmth and an increased secretion of sweat. This erythema in higher grades or in susceptible individuals may lead to exanthemata.[1]

Much has been written about the effect of morphin on the *circulation of the brain*, but the definite information on the subject is very small. Of course, when it comes to a fall in the general blood pressure, the circulation of the brain will also be diminished, but there is no proof of any direct action on the cerebral vessels.

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[1] Other poisons which may produce erythema are: atropin, quinin, chloral, coal-tar products, iodids, bromids, etc.

(*c*) *Pupil.*—In man, morphin-poisoning is usually characterized by a contraction of the pupil (*miosis*). This is due to the *paralysis of the medullary pupillodilator center.*

The effects of drugs upon the pupil will be more fully discussed in Chapter XI. Suffice it to say that an effect may be either central or peripheral. The distinction may be made by stimulating or dividing the nerve-trunks going to the iris. If the change persists, if it can be obtained on an excised eye, and appears more marked on local application, it must be peripheral; whereas, in the contrary case it must be central.

With morphin the dilatation occurs after systemic, but not after local application, and it does not occur on the enucleated eyeball. It is therefore *central.*

It might then be due either to a stimulation of the constrictor center or to a depression of the dilator center. It is probably paralytic, for most of the other effects of morphin on the medulla are paralyzing, and the miosis persists in the highest grades of poisoning, when stimulation would scarcely be possible. Further, in those animals in which morphin has an excitant action (cat), it produces dilatation instead of contraction.

This miosis has no therapeutic importance, but is of some interest in the differential diagnosis of coma.

(*d*) Several effects of morphin are probably, at least in part, due to its medullary action: thus, salivation, vomiting, sweating, etc. These will be considered later, since the central nervous system is only one of the factors involved. The *sweating* is entirely secondary to the dilatation of the cutaneous vessels and later to the asphyxia. The *temperature* center is also depressed, so that the animal does not so readily accommodate itself to changes in the surrounding temperature.

(C) **Effects upon the Spinal Cord.**—These have been studied for the most part on frogs, in which they are not so largely obscured by the action on the higher centers. In these animals it produces a slight primary depression. This is followed, with small doses after several days, by a strychnin-like condition, a *secondary tetanus.* This secondary tetanus is never seen in susceptible mammals because doses required for it will kill the animal before there is time for its production. Most warm-blooded animals show only an *increase in the reflex excitability*, which comes on early and persists. (Strychnin is, therefore, not a good antidote.) This forms quite a conspicuous symptom in all animals.

One would be tempted to explain this increased reflex excitability by the removal of the inhibitory influence of the higher centers, and this is certainly one factor. But the results are much larger than could be produced in this manner, and a direct stimulant action on the cord must be assumed.

Aphrodisiac effects are partly due to stimulation of the cord, partly to the effect on the imagination.

In reference to the predominance respectively of the strychnin-like action on the cord, and the narcotic action on the brain, the members of the group can be arranged in the following series :

Narcosis predominates :
↑ morphin
heroin
papaverin
codein
narcotin
↓ thebain.
Tetanus predominates :

The **cause of the action of morphin** on the central nervous system is very imperfectly understood, just as is that of all other alkaloids. It has been attempted to explain its action by a *change in cerebral circulation*, but this change comes late and is seen only with the largest doses. But even if this explanation were true, it would not give any real insight into the cause of the action, but only advance the question one step further: for this itself would be due to depression of the vasomotor center. The same discussion has been going on in regard to natural sleep.

Others have sought for *histologic changes*, but with the present methods, unsuccessfully.[1] As to *gross changes* in the brain, almost all drugs which cause narcosis or tetanus are said to produce hyperemia of the membranes, often also some effusion into the ventricles.

2. Peripheral Actions.—(a) Morphin and other members of the group have practically *no action upon muscle- or nerve-fibers or endings.* Particular stress must be laid on the fact that the *sensory endings are in no way affected*, so that the local application of morphin or opium is entirely irrational.

But this is a practice which clinicians seem very loath to renounce, and lotions and local injections containing morphin are still very frequently employed. The apparent good results obtained are largely due to the absorption of morphin from wounds or mucous surfaces. It can even be absorbed to a slight extent from the unbroken skin. The most popular form of this local use is the lead and opium wash, and this certainly gives satisfactory results. The effects are probably to be explained by the non-irritating covering furnished by the lead precipitate, and by the astringent action of the lead itself.

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[1] The histologic methods which might be employed in such investigations are so delicate and complicated that they require a great deal of practice, and can be carried out only by those who have devoted themselves for a considerable time to this line of research, and even then a certain amount of doubt is permissible.

The direct application of codein destroys the activity of nerve ganglia and nerve-fibers.

(b) Effects upon the Alimentary Canal.—*Stomach.*—Morphin, no matter how administered, impairs the digestion and tends to produce nausea, vomiting, and salivation.

One might be tempted to ascribe these effects to its central action, but morphin is excreted very rapidly into the stomach, and local action cannot therefore be excluded. There is, however, little direct evidence on this subject, and it is quite possible that both central and peripheral action are involved.

Heroin produces only salivation and no vomiting, and usually little, if any, gastric disturbance—facts which point to a central action.

The action of morphin upon **peristalsis** belongs to the best-known, and at the same time the least understood, of its effects. In man it produces constipation in practically all doses, except the very largest.

In these it causes bloody stools, probably through vasomotor paralysis.

In animals, however, its effects are quite variable, according to the species and other conditions, so that one may see almost any action. In the dog it usually causes diarrhea. Results obtained on this animal cannot be applied to man at all.

The difficulties in the study of these phenomena lie not only in the difference in the animals, but also in the ease with which peristalsis is influenced by the slightest disturbing factors; and in the complex innervation of the alimentary canal. Our knowledge of the latter subject has been revolutionized within the past few years, and cannot even now be considered in a satisfactory condition. As to the action of drugs, most of the work which has been done is old, and needs a thorough revision in the light of our present knowledge.

The peristalsis is very greatly affected through changes in the circulation which are not very easy to control and to interpret. When the abdomen is opened, as is necessary for an analysis of the phenomena, the exposure to the air, or to the salt solutions, which are probably not quite indifferent; the abnormal conditions of pressure; the inattention to exact regulation in temperature; the setting-up of direct or reflex stimulation or inhibition by the unavoidable handling of these organs or by the attachment of apparatus; the relative difference in longitudinal and circular coats in different animals; the nervous supply, which is perhaps quite different in different species; the variable activity of the central nervous system;—all these are complicating factors which seem to influence the results in an extremely strong manner, and which it is absolutely impossible to exclude.

In man the most important factors concerned in peristalsis are probably the following:

1. A local mechanism which seems to consist of a complete reflex arch, the nervous center of which is located in Auerbach's and Meissner's plexus.

2. A certain power of irritability and of rhythmic contraction residing in the unstriped muscle itself.

3. The activity of both of these is influenced by the local conditions of circulation.

4. A central control consisting of:

(*a*) tonic inhibitory impulses passing down the splanchnic to the local centers;

(*b*) both inhibitory and augmentor fibers contained in the vagus; the latter are not tonically active and are very easily eliminated by other influences.

Contraction of the circular coat of the intestine will diminish the lumen; of the longitudinal coat, will shorten the gut, and may compress it. The latter, however, is not sufficient to be of importance. The coats seem usually to act synchronously.

Two kinds of motion can be distinguished in the intestines removed from the inhibitory influences of the splanchnics by section of these nerves.

1. A rapidly advancing *rhythmic pendulum movement* affecting longitudinal and circular fibers simultaneously, myogenic in origin, and probably propagated by muscular conduction.

This movement is probably not concerned in the propulsion of the intestinal contents, and is, therefore, of little practical importance.

2. *Peristalsis.*—This travels much more slowly, and is a true coordinated reflex, started by mechanical stimulation of the intestine and carried out by the local nervous mechanism. It occurs independently of the connection of the gut with the central nervous system, but may be restrained by the latter. It travels only in one direction,—*i. e.*, descends,—and consists in two phases, a constriction above the point of stimulation and a dilatation below it.

The physiologic importance of this arrangement will be readily appreciated, for by it the resistance to the downward passage is removed, whereas the constriction above forces the mass to descend.

These peristaltic movements can be very easily started in a portion of the intestine removed from the influence of the splanchnics, but only with difficulty when the latter are intact.

Local anemia of the intestine inhibits all the movements observed in the isolated intestine of the dog. Any condition, therefore, which causes a fall of blood pressure will tend to diminish the intestinal movements. In the rabbit, on the other hand, peristalsis is stimulated by local asphyxia.

In view of these complicated factors the study of the effects of drugs upon the peristalsis is very unsatisfactory. The following schema may be looked upon as a provisional method of studying these actions:

(A) *Lessened peristalsis* may be due to:

1. Paralysis of the muscles: physostigmin will have no effect.
2. Paralysis of Auerbach's plexus: nicotin will have little effect, but physostigmin will produce contraction. Mechanical stimulation after section of the splanchnics will have no effect.
3. Stimulation, direct or reflex, of the splanchnics. There will be no effect if the drug in question is used after section of the splanchnics.
4. Fall of blood pressure: the effect will be proportional.

(B) *Increased peristalsis* may be due to:

1. Stimulation of the muscles: the effect will consist of local contraction rings which will not be inhibited by nicotin.
2. Stimulation of Auerbach's plexus: peristalsis spreads and is inhibited by nicotin.
3. Inhibition of the splanchnics: the effect is not obtained if the drug is used after section of these nerves.
4. Increased circulation: the effect is abolished if the pressure is returned to normal.

The *large intestine* has a mechanism similar to that of the small; the importance of the local mechanism, however, decreases toward the lower portion of the gut and is not concerned in defecation, the central mechanism becoming more prominent. The sympathetic is here also inhibitory, the motor nerve for both coats being the pelvic visceral.

With *morphin* the most suggestive results are observed on the rabbit.

The application of a crystal of NaCl to the muscular coat of the unpoisoned intestine produces a constriction above the point of application—*i. e.*, the effect is identical with that produced by mechanical stimuli, and is, therefore, due to stimulation of Auerbach's plexus. (A crystal of KCl, on the other hand, produces a constriction ring which remains confined to the point of application, and is, therefore, myogenic in origin.)

Small doses of morphin prevent the spreading of the NaCl stimulation even when the mesenteric nerves have been divided. Its action is therefore peripheral, and must consist in either stimulation of the splanchnic endings or paralysis of Auerbach's plexus; very probably the latter. But large doses of morphin do not have this effect, and this makes any explanation extremely unsatisfactory.

Heroin does not affect the intestine.

Those are all the facts known at the present regarding this matter, and all that they teach is, that with man and certain animals morphin diminishes peristalsis by some peripheral action, probably through paralysis of Auerbach's plexus; whereas with other animals it increases peristalsis, probably also through a peripheral action.

This action is obtained better with opium than with morphin on account of the greater local action of crude drugs as compared with alkaloids.

(c) **Secretions.**—Our knowledge in regard to this subject is also unsatisfactory. Whilst morphin generally tends to check the salivary as well as the bronchial secretions, yet the saliva is very frequently increased. When this occurs in early stages, it may be attributed to nausea, but it sometimes occurs rather too late for this explanation to hold, and it is possible that the medullary salivation center is involved. The sweat is increased through the erythema.

Heroin also increases saliva and sweat.

The *appetite* is diminished on account of the lessened perception of hunger and through gastric derangement.

(d) **Metabolism** is also lessened on account of the quiet condition of the animal and, in prolonged observations, on account of the disturbed digestion. The CO_2 is increased in the blood through the asphyxia. The nitrogen excreted is also lessened. That the lessened output of CO_2 is really due to depression is shown by the fact that it is increased in the cat. The asphyxia also causes glycosuria.

III. ABSORPTION, FATE, AND EXCRETION.

Morphin is readily absorbed from all surfaces, and to some extent even from the unbroken skin. Its further fate was for a long time problematic. Although contradictory claims have been made, it is now conceded that only the very faintest traces, if any, are excreted through the urine. Nor does this contain any morphin derivatives. Recent investigations have shown that after hypodermic injections up to 66% is excreted through the intestine. This large percentage holds only for acute poisoning. It is very much reduced in chronic poisoning, as will be described under that heading.

Some of the morphin is also excreted by the milk and may cause morphinism in sucklings. The rest is decomposed in the body.

Some interesting problems, so far unsolved, arise in this connection: What are the end products? Are the changes the same in frogs as in warm-blooded animals? In what organs does the decomposition take place? In regard to the last, it has been shown that it is not destroyed when blood containing it is circulated through the spleen or liver.

The substances which cause the characteristic odor of opium are excreted largely by the urine, and to some extent also by the breath, sweat, and milk.

IV. COMPARISON OF MEMBERS OF GROUPS.

The other members of the morphin series, as well as those of other Papaveraceæ, serve as connecting links between strychnin and chloral.

This is illustrated in the following table, which also shows by → the relation to the cocain and curare groups:

Narcotic action predominates:
↑ Chloral
* Protopin, Cryptopin, Chelidonin, →Cocain, Homochelidonin, and Chelerythrin
Morphin: takes about central position
Papaverin
Heroin
Codein
Narcotin
* Sanguinarin
Thebain
Laudanin
Brucin
↓ Strychnin →Methyl-strychnin, Curare.
Stimulating action predominates:

It will be seen that, through its narcotic action, morphin is related to the alcohol group and to Cannabis Indica; to the latter also through its stimulating action on the higher and motor centers. Through its stimulating action on the cord it is related to strychnin. A sub-class of this group, the protopin group, also establishes a connection with cocain, in paralyzing peripheral sensory nerves.

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*Protopin group.

The members of the **protopin group** (protopin, cryptopin, chelidonin, homochelidonin, and chelerythrin), which are found to some extent in opium, but especially in other Papaveraceæ, cause paralysis of the sensory endings in the manner of cocain. They also produce a paralytic change in the striped muscle endings, so that stimulation with interrupted current only produces a series of very rapid and complete contractions and relaxations instead of a continuous tetanus. The heart muscle is also depressed, so that the heart is weak and slow. The respiration is stimulated.

A preparation of sanguinaria examined by the author had very little action on the heart, and was purely depressant to the central nervous system, the reflexes being diminished, the respiration slow and shallow, and death occurring through respiratory paralysis. No secondary tetanus was noticed on the frog. This interesting drug requires further investigation.

With the exception of sanguinaria, the members of this group have little or no therapeutic importance.

V. CHRONIC OPIUMISM.

The first authentic record of the habitual use of opium falls in the beginning of the sixteenth century. It is mentioned in 1511 as an important article of import from East India. In 1516 its extensive habitual use in Cochin China is recorded. From this time on, mention becomes more frequent. It would seem that its use is much older in India than in Turkey, and that the Mohammedans learned it through the conquest of the former country. Their acquaintance with Haschisch is of much earlier date.

Opium users introduce the drug in three different ways: by smoking, by eating, or by hypodermic injection of morphin. Smoking is the form mainly practised in the East, and is not uncommon in the United States. A perfumed solid watery extract is smoked with a special apparatus. This manner of using opium produces a form of intoxication differing from that of alcohol in that it causes greater energy, vividness, and sharpness of imagination. The half-conscious victim is removed from the unpleasant reality into a realm of glowing fancy, in which he visits the highest heavens; but only to awaken in a few hours to sensations similar to, but much worse than, those following alcoholic excess. There is but one relief for his miserable sensations —more opium—which he takes until his supply of money is exhausted.

The consequences are similar to those of other forms of opium using, but smoking seems rather more firing to the imagination, perhaps because of the stimulating effect of the smoke itself. It is less disturbing to the alimentary canal because the alkaloid does not come into such direct contact. Besides, the quantity consumed in smoking must necessarily be more moderate.

This description of the bad effects applies mainly to the European races. Curiously enough, Eastern races are not affected in the same way. They smoke opium more as a European smokes tobacco. Though, of course, incapable of doing work while under the influence, the lethargy need not last longer than half an hour, when they can resume their business. Nor do they show the moral degenerations so striking in the Western users.

Opium eating and the hypodermic use of morphin show exactly similar phenomena and sequels. These forms of morphinism cannot even boast of the delusive pleasures of smoking, though it cannot be denied that opium, even when taken by the mouth or through the skin, produces at first some of that somewhat negative pleasure which consists more in a brutish indifference to surroundings than in any actual enjoyment. In smaller doses the capacity for enjoyment may even be increased, just as with alcohol, by removal of the ordinary restraining impulses. But, not to mention the final cost, even this pleasure soon fades, and ere long the famed dreams of the opium eater degenerate into nightmares quite as bad as those of delirium tremens. The opium eater now takes his drug not because he wants it, but because he cannot get along without it. When it has once taken a thorough hold, morphinism must be considered not so much as an indulgence, a pleasure, or a vice, but as a real disease. The organism having become accustomed to working under its influence, revolts in a very violent manner against its withdrawal. Symptoms result which are something fearful objectively; there are neuralgias, digestive crises, and even dangerous collapse, and, subjectively, sensations simply terrible to the patient, but apparently incapable of description.

One of the most striking and instructive facts in this opium habit is the remarkable tolerance which is acquired toward the poison. Quantities, which with ordinary individuals produce death with absolute certainty, are borne with immunity. The largest daily quantity of morphin reported is 5.5 Gm., which equals 85 grains, or one and two-thirds of the ordinary bottles. Even larger doses are mentioned by men in charge of institutions for treating morphinism.

Too much weight must not be attached to the statements of the patients, for these go to such an institution with the theory that their daily quantity will be cut down a certain percentage and that their allowance will be the larger, the more they claim to be using.

But the fact stands absolutely unquestioned that extraordinarily large doses can be taken daily without producing acute symptoms, and are even necessary to prevent the withdrawal symptoms. This immunity to morphin is, however, never absolute, and death from overdoses forms the most frequent " excitus letalis " of the morphinist.

The abstinence symptoms are something very difficult to explain, and so far they have been demonstrated only with morphin and cocain.

It has been suggested that these symptoms are produced by products arising through the decomposition of morphin in the body. These products have, according to this theory, an action antagonistic to morphin, so that the greater amount of morphin introduced would be used in neutralizing their action, but would by its own decomposition again increase the amount to be neutralized. It is claimed that one of the oxidation products of morphin, oxydimorphin, has such an action, and that it is found in the excretions of morphin patients. Both these statements have, however, been contradicted, and are probably incorrect.

The tolerance is explained by the *increased power of the organism to destroy the poison.*

Faust, in a recent research on this subject, recovered from the feces of a dog 66% of the morphin administered hypodermically, when the poisoning was acute. In the feces of the twenty-first to twenty-fourth day of the administration he only recovered 26% ; from twenty-nine to thirty-two days, 8% ; from thirty-six to forty days, 4% ; and if still longer continued, none at all ; and this notwithstanding the fact that the later doses were very much larger than the original doses (fifty times the original amount). Incidentally, he found exactly the same symptoms of chronic morphinism in the dog as exist in man. The animals showed signs of uneasiness for the morphin, they became very restless when the time for the injection approached, and one dog gave every sign of satisfaction when the syringe was introduced ! Tolerance was soon established, so that after twenty days a dose ten times as large as that which originally gave a very strong effect had little action.

It is, of course, permitted to assume the production of an antivenom which causes this increased destruction of the morphin, and it has been claimed that the serum and leucocytes of an habituated animal immunize against the acute effects of morphin. This statement needs confirmation.

While it seems, therefore, that the attractive theory advanced to account for the abstinence symptoms—namely, that they are due to the formation of a toxic substance (oxydimorphin)—must be abandoned, the fact still remains that opium users can be blamed only for the first step, and deserve only pity for the continuance of the habit.

The later *consequences of opiumism* are insidious, but none the less dangerous. For years, victims of the habit may appear quite normal to superficial observers, but closer attention would even then reveal signs of the disease. The physical consequences relate at first to the digestive tract. There is obstinate constipation, alternating later with equally obstinate diarrhea. There is loss of appetite alternating with voracious hunger and thirst (polydipsia), and polyuria. These disturbances of digestion, as well as the more direct action of the drug, are not long in showing their effects upon the rest of the body. The patient loses flesh rapidly and suffers from marasmus and cachexia.[1]

There is a peculiar cirrhosis of the skin, and the condition of the integument is rendered still worse by the local effects of the injection when the drug is used hypodermically. The whole skin may be mottled with scars and marks of recent or older injections, and abscesses are often produced through want of cleanliness. Even when the drug is used by the mouth, the entire skin often acquires a peculiar waxy appearance.

Other physical disturbances also exist. The pupillary and accommodation movements are affected. The *heart* is irregular. *Albuminuria*, *glycosuria*, *amenorrhea*, and impotence are frequent. *Fevers* resembling simplex, intermittent, and typhoid, are often seen. The *motor-nervous system* also shows considerable change: nervous tremors, increased reflex irritability, etc. These conditions sooner or later weaken the resisting powers of the patient, so that he falls an easy prey to some other ailment, and thus rarely reaches old age.

The effects of the opium habit upon the *character* of the patient are even more deplorable. This soon sinks to the very lowest level. With a certain amount of low cunning he combines a total unscrupulousness, and it is very doubtful whether the testimony of an opium user can ever be accepted, even in instances which do not affect him. He becomes absolutely incapable of any effort. Duty no longer appeals to him, and in order to escape it, or, still more, in order to obtain his drug, he will resort to any lie or any trick, no matter how dishonest. He will promise everything and fulfil nothing. Were he not so cowardly and disinclined to, or rather incapable of, any effort, he would be fit for any crime. His condition is all the more unhappy since he fully realizes it and sees himself in his true colors. He makes grand plans, and, at the same time, knows that he can never summon the energy even to begin them. Add to this the fact that he is a social outcast, and it is difficult to imagine a more unhappy condition. To the physician he should appeal as a sufferer, as one afflicted with a form of insanity; one who, like any other insane patient, should be treated with unflinching firmness, but with the most considerate kindness. Only in this way will it be possible to help him. He is himself devoid of the necessary will power, and this must to some extent be supplied by his physician and attendants. In this connection, as in the other drug habits, suggestive therapeutics offers a promising prospect, but has not perhaps been sufficiently tried to permit a final judgment as to its value. As to the ordinary medical **treatment,** this may be summarized under two headings: *removal of the drug; and supporting and symptomatic measures.* The **removal** must be done with great care, and is best carried out in special institutions, where a careful surveillance of the patient is possible, both to prevent his obtaining an extra supply of the drug, and to be able to control the symptoms. It has been attempted to stop the habit by removing the drug suddenly; by very gradually diminishing the doses; and by diminishing the dose quite rapidly. The first is useless cruelty, and may even be dangerous. The second does not usually accomplish the desired result. The last is certainly the best. According to this method, the drug is removed just as rapidly as can be borne by the patient without producing any very violent reaction. No iron-clad rule can be followed by which this reduction may be accomplished. At the same time the system is built up by proper *hygienic measures.* The appetite often needs to be sustained by bitters and other tonics. Sleeplessness is a very frequent complication, and must be met by bromids, chloral, or some of the hydrocarbon hypnotics. To combat morphinism by cocain, codein, heroin, or other drugs which merely replace the morphin habit by some other habit equally bad, is of no benefit to the patient. Thorough cleansing of the bowels with emetics and cathartics at the beginning of the treatment is very useful, and it is perhaps to this that pilocarpin owes its success. This drug has been employed on the theory that it removes the hypothetic decomposition products. As far as may be judged, it has given good results, whatever the explanation.

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[1] These are two ill-defined terms. The former, marasmus, signifying a continued low condition of the nutrition and a wasting of the flesh without apparent organic cause. Cachexia also indicates a wasting of the body, with some striking change in the features, which are usually pinched and yellow.

The cure is rarely permanent. Patients usually drift into the morphin habit to relieve some existing condition,—*e. g.*, sciatica,—and this condition will, of course, reappear when the morphin is removed and then force them to again begin its use. And besides, persons who have once been morphinists show by that fact that they are more apt than normal individuals to succumb to the dangers that originally overcame them.

Opium habit in children is unfortunately not at all rare, and it is usually started by indiscriminate employment of paregoric and other soothing syrups. They present the typical symptoms already described. Withdrawal of the medicine is followed by restlessness, wakefulness, and every indication of suffering and distress. The treatment would be mainly hygienic.

VII. TOXICOLOGY OF MORPHIN AND OPIUM.

Opium is a very frequent means of suicidal poisoning, and accidental overdoses are not at all rare. It is, however, one of the rarer poisons in criminal cases, since its action is so slow and the symptoms so typical.

Symptoms.—To sum up the symptoms of morphin- or opium-poisoning from a toxicologic point of view, the first to be noticed are giddiness, confusion, and stupor, this terminating gradually in complete insensibility. The respiration is slow, the pulse full, slow, and laboring, eyes closed, pupils usually contracted and insensible to light, and the face red.

As the poisoning advances the skin becomes pale and cold, and moist with perspiration, the lips are livid, the breathing slow and stertorous, the pulse feeble and almost imperceptible, the limbs relaxed; but death is sometimes preceded by asphyxial convulsions.

The symptoms usually appear in from ten minutes to one hour after the drug has been taken by the mouth; perhaps half an hour is the most common. Death occurs in from two to twelve hours.

If the patient *recovers*, there is a great deal of persisting nausea, nervousness, and headache. With therapeutic doses, however, the patient may awaken refreshed. Recovery is possible even when convulsions and coma have set in. The former disappears and the coma gradually passes into a long sleep, often lasting from twenty-four to thirty-six hours.

On account of the treatment, it is extremely important to establish the **differential diagnosis of the origin of a coma.**[1] Those forms of coma which might be confounded with morphin are: alcoholic (chloral), uremic and diabetic, epileptic, and apoplectic.

One of the most important points is furnished by the **pupils.** If these are *dilated*, the coma is probably *alcoholic*, but may be diabetic. With *pin-point pupils* the coma is either from *opium* or *pontine apoplexy*. If the latter, they are very often unequal, and on lifting the arms, one may often detect a paralysis.

The pupils respond readily to light in epileptic coma, not in the others.

Just before death the pupils become dilated from the asphyxia. (In the dog the pupils are usually dilated throughout the poisoning.)

The *smell of the breath* furnishes presumptive evidence of *alcohol*-poisoning, but it is not a definite proof, since this substance is often given as an antidote, and is so often present in quantities which would not cause a coma. The smell is, however, usually characteristic of *opium*, *uremia*, and *diabetes*, but not of morphin. Uremia would also be characterized by *albumin in the urine*.

There are yet other forms of coma which may be confused with these, but no rules can be laid down for them. The history is often of the greatest importance.

The *autopsy* shows nothing characteristic. There are the usual phenomena of asphyxia. The pupils are variable. The mucous membrane of the stomach is sometimes reddened. If the poisoning has been by opium, one may discover its characteristic odor.

Treatment of Acute Opium-poisoning.—The first indication is to *empty the stomach*, and this no matter whether the drug has been taken by the mouth or hypodermically. If narcosis has already set in, emetics may act too slowly, and it may be necessary to employ a stomach-pump. The patient should be kept awake as far as possible and in *constant movement*, since this contributes to the better tone of the medullary center. Other *general reflex stimulants* may be employed, such as *cold ablations*, the inhalation of *ammonia* in the form of smelling salts, hypodermic injections of ether, etc. Caffein, especially in the form of strong, black, hot *coffee*, is the best antidote, and given in this way the tannin is also useful. *Potassium permanganate* has lately been warmly recommended. It is, of course, only efficient on that portion of the poison present in the stomach, and then only if the stomach is empty.

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[1] Coma: A condition of insensibility from which the patient cannot be aroused.

Another physiologic antidote is *atropin*, which also stimulates the upper portion of the central nervous system.

The antagonism exists only if the doses of both poisons are comprised within definite limits. A *dose* of 1.5 mg. ($\frac{1}{40}$ grain) of atropin sulphate should be given as soon as possible, and this should *not* be repeated.

The patient should be kept *warm*. If the breathing shows signs of failing, artificial respiration should be supplied.

When the danger is over, the *constipation* which usually follows should be relieved by cathartics and enemata.

The *fatal dose* of morphin for man is, on the average, 0.4 Gm. (6 grains); or of opium, 3 Gm. (45 grains). The possibility of idiosyncrasy must be borne in mind: as little as 0.2 Gm. (3 grains) of opium (= $\frac{1}{2}$ gr. morphin) is said to have been fatal in one case.

The fatal dose of morphin for dogs, given intravenously, is 0.1 Gm. per kilo of the hydrochlorate; hypodermically, 0.15 Gm. Pigeons are very tolerant.

VIII. THERAPEUTICS.

Morphin and opium are drugs which are used against *conditions*, and not against *diseases*; *i. e.*, they may be employed in almost any disease if the conditions demanding them arise.

The conditions indicating morphin are mainly the following: *to lessen pain, to produce sleep, to check peristalsis, and to suppress cough.*

1. **Pain.**—Since the lessening of pain is its first effect, small doses only should be employed for this purpose. It will be remembered that it is effectual especially against persistent pain, and in this it is almost specific, surpassing in analgesic action any other drug. Hence, *pain always indicates morphin.* The local application is of no advantage. As an analgesic morphin, especially hypodermically, has the preference over opium.

2. **Insomnia.**—Morphin will be useful especially when this is produced by pain, but not when it is the result of

nervousness. Besides its superior analgesic properties it surpasses chloral in not affecting the circulation. The two are very usefully combined.

Some of the disadvantages of opium are: the tendency to constipation, to nausea, or gastric disturbances; and in some individuals it has an excitant action instead of being hypnotic. In insomnia one must be ever mindful of the danger of the formation of a morphin habit.

3. **Peristalsis.**—Opium especially is extremely useful in diarrhea due to acute intestinal catarrh. By checking the peristaltic movement, it gives a chance for rest and repair, and thus leads to permanent cure. It is one of the most important ingredients of the so-called cholera-mixtures. In the constipation of lead-poisoning which is due to tetanic contraction of the intestine, it relieves this spasm, and with it the pain. It is also very useful in *peritonitis* in relieving the pain, both directly and by lessening the movements of the intestines which are giving rise to it.

Tyrotoxicon-poisoning is an exception, for in this morphin is only harmful.

4. **Cough.**—Morphin and other members of the group depress the sensibility of the respiratory center to reflex stimulation, and morphin also diminishes the amount of bronchial secretion.

In bronchitis the cough is caused by reflex stimulation of the center. The patient also involuntarily uses the shallow respiration, since deep respiration brings on coughing. These conditions are removed by members of the morphin series, which at once lessen the tendency to coughing and affect the respiratory center in such a way as to slow and deepen the respiratory movements. As to particular members of the group, codein was formerly often used because it is devoid of the intestinal action of morphin. In recent years it has been superseded by heroin, as this causes no headache or gastric disturbances and presents the least danger. There is as yet very little known about the dangers of a heroin habit.

When the bronchial secretion is extremely abundant, morphin may be contraindicated, for then the cough fulfils a useful function in cleansing the air-passages.

Morphin is frequently of considerable usefulness in *asthma* in relieving the distress of the patient, and perhaps also by diminishing the reflexes which give rise to this condition. (Strychnin is also useful in this condition by putting the center in a better state when it has been fatigued.)

5. **Other Uses of Morphin.**—Morphin is very useful as an introduction to *general anesthesia*, given hypodermically in a dose of 0.01 Gm. (1/6 grain), one-half hour before the

administration of the anesthetic. It lessens the amount of the anesthetic necessary. It is very often mixed with a small dose ($\frac{1}{100}$ grain) of atropin, the latter for the purpose of paralyzing the vagus endings in the heart.

Psychic exaltations—*e. g.*, delirium tremens or atropin-poisoning—require very large doses, which might become dangerous. It may, however, be used in atropin-poisoning, whereas in delirium tremens it would not be indicated because it itself increases the nervousness.

It is used in *tetanus* for the purpose of removing the pain.

Morphin forms quite an efficient *diaphoretic*. For this purpose it is best given combined with ipecac in the form of *Dover's powders* against *colds*, etc. (See Chapter XII, M). Heroin, on the other hand, is recommended against the night-sweats of phthisis.

Morphin has also been used as an *anti-emetic*. It may be conceived that it is of benefit in depressing the vomiting center, but it is quite uncertain, and may itself produce emesis. Some members of the group are even used as emetics, *e. g.*, **sanguinaria**, but this drug also contains an irritant principle, which no doubt contributes to its action. S. is useful as a *nauseant expectorant* in cough, where it also depresses the respiratory center.

Opium is also employed as a *styptic* to stop hemorrhage in inaccessible situations. Its action can be explained by the lessening of movements which it favors, and consequently the easier formation of clots.

Besides in those diseases already mentioned, morphin is useful in the following: *Phthisis*, through its action on the cough, bronchial secretion, and hemorrhage ; *fever*, through its diaphoretic and hypnotic action. It has also been used in *malaria*, but with doubtful results.

The use of opium in **diabetes** is instructive in showing that a drug may relieve not only one, but several, symptoms of a disease, and still be only symptomatic, and not curative.

Good clinical observers claim that the thirst, polyuria, glycosuria, and itching of the skin are all markedly diminished. Part of this action must be attributed to the analgesic effect, while the influence on the glycosuria is due to its action on digestion, and is produced in the same way as by a limitation of the diet or by nauseants. As a matter of fact, opiophagic diabetics die faster than others. Codein has been used instead, but without any marked advantages.

Glycosuria is only one symptom, which results from various, and as yet imperfectly understood, causes. Each causal condition probably requires a different treatment, but only the symptoms are comparatively accessible to medicines. Of these symptomatic measures, opium is perhaps the *least* harmless. A much more recommendable measure, producing results in the same way, as has been said, is the modification of the diet; that is, the exclusion of carbohydrates from the food. This is of considerable value in fat persons, especially since the limitation of diet favors complete oxidation of the existing material; but to starve an emaciated person must be considered a mistake.

The regulation of the diet should be arranged in such a way as to exclude carbohydrates as far as possible, and the proteids as little as possible. There is, however, a point beyond which carbohydrates cannot be reduced with profit; for reduction beyond this limit favors the production of oxybutyric acid and acetone, a most dangerous process, since this is probably the main cause of diabetic coma. The limit must be determined empirically; *i. e.*, carbohydrates should be entirely withdrawn until the glycosuria has reached its minimum, and then should be gradually increased until there is a marked rise of the sugar in the urine. They can then be kept a little below this point.

Sugar should be excluded from the diet altogether and be replaced by saccharin or glycerin, which are not carbohydrates; instead of the ordinary bread made from flour, a bread made from gluten, and therefore starch-free, can be used.

Although this is purely symptomatic treatment, it seems not only to lessen the sugar in the urine, but also to cause an improvement in the general condition of the patient. This may perhaps be explained by assuming that the faulty oxidation of the sugar goes hand in hand with the production of other noxious products.

Since the underlying causes of diabetes are connected with metabolism, many drugs which have an influence on the latter have been tried empirically, and may give good results in certain cases. The subject is still too obscure to permit of judging beforehand whether the effects of certain drugs will be desirable. Such drugs are: arsenic, quinin, iron, phosphorus, etc. When the diabetes is connected with syphilis, mercury very often gives good results. Vanadium salts have recently been introduced by French clinicians, but have hardly been sufficiently tested.

Still another way of affecting the oxidation is by means of exercise—the proper amount being determined by experiment.

Cathartic salts are also useful, perhaps, in removing waste products and toxins from the alimentary canal and improving the digestive functions. They are best given in the form of alkaline salts (bicarbonates or carbonates), since these prevent the tendency to the development of diabetic coma by neutralizing the oxybutyric and other acids which are the cause of this condition. (See Chapter XXVI.)

IX. MATERIA MEDICA.

⁂ **Opium** (U.S.P., B.P.).—*Opium* (Meconium, Thebaicum).—The dried milky juice exuding from the excised unripe seed-capsules of the poppy, *Papaver somniferum*, Papaveraceæ. Asia and Egypt, cultivated. Fair samples have also been obtained from plants cultivated in California and Minnesota, but the price of labor makes its production unprofitable. The plant is often cultivated in gardens. The proportion of active ingredients varies greatly in different samples.

The *capsules* (Papaveris Capsulæ, B.P.) and *seeds* also contain the active principles, and are sometimes used. The seeds contain, in addition, 50% of a bland fixed oil, which may be used like olive oil.

Alkaloids: Morphin. Official requirement (U.S.P.): More than 9% in moist opium, 13 to 15% in powdered opium; B.P., 9½ to 10½%.
Codein, 0.2 to 0.7%.
Thebain, 0.15 to 1% (belongs to strychnin group).
Narcein, 0.02 to 0.7%.
Papaverin, 1%.
Narcotin, 1 3 to 10%.

Meconic and lactic acid, gums, resins, fats, odorous principles. No starch or tannin.

Dose: 0.015 to 0.12 Gm. (¼ to 2 grs.).

Preparations:

⁂ *Opii Pulvis* (U.S P.).—*Dose:* 0.015 to 0.12 Gm. (¼ to 2 grs.).

Opium Deodoratum (U.S.P.).—The opium is exhausted by ether and mixed with milk-sugar so as to contain 13 to 15% of morphin. The purpose of this manipulation is to remove the narcotin. It is not very popular. *Dose:* 0.015 to 0.12 Gm. (¼ to 2 grs.).

Preparations Containing Crude Opium.

Pilulæ opii, U.S.P.: Each 1 grain of opium.

**Pilulæ opii et camphoræ*, N.F.: Each 1 grain of opium and 2 grains of camphor.

**Pilulæ opii et plumbi*, N.F.: Each 1 grain of opium and 1 grain of lead acetate.

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* Not official.

The most important preparations are marked ⁂.

Pilula Plumbi cum Opio, B.P., contains 12.5% of opium. *Dose:* 0.1 to 0.25 Gm. (2 to 4 grs.).

Pilula Saponis Composita, B.P., contains 20% of opium. *Dose:* 0.1 to 0.25 Gm. (2 to 4 grs.).

⁂ *Pulvis Ipecacuanhæ et Opii*, U.S.P. (*Pulvis ipecacuanhæ comp.*, B.P.), contains 10% each of opium and ipecac. *Dose:* 0.3 to 1.0 Gm. (5 to 15 grs.).

Pulvis Kino Compositus, B.P., contains 5% of opium. *Dose:* 0.3 to 1.3 Gm. (5 to 20 grs.).

Pulvis Cretæ Aromaticus cum Opio, B.P., contains 2.5% of opium. *Dose:* 0.5 to 2.5 Gm. (8 to 40 grs.).

Suppositoria Plumbi Composita, B.P., contain 1 grain of opium.

Other Solid Preparations of Opium.

Extractum Opii (U.S.P., B.P.). Made with water; contains 18% morphin (U.S.P.) [20%, B.P.]. *Dose:* 0.008 to 0.06 Gm. (⅛ to 1 gr.).

Emplastrum Opii (U.S.P. = 6% of the extract; B.P. = 10% of opium).

Solutions of Opium, U.S.P.

The following U.S.P. preparations all contain 10% of powdered opium and have a *dose* of 0.2 to 1.2 c.c. (3 to 20 ♏); all are miscible with water or alcohol:

⁂ *Tinctura Opii* (Laudanum): Made with one-half alcohol.

Tinctura Opii Deodorati: Made with one-fifth alcohol after exhaustion by ether. (This is similar to McMunn's Elixir and other patent preparations.)

Acetum "
Vinum "

Compound Liquid Preparations Containing Opium.

For Internal Use:

Tinctura Ipecac. et Opii, U.S.P.: Opium and ipecac each 10%; one-half alcohol. *Dose:* 0.2 to 1 c.c. (3 to 15 ♏).

⁂ *Syrupus Ipecac. et Opii*, N.F. (Dover's syrup): Each dose, 4 c.c. (1 drachm) = 0.35 Gm. (5 grains) of Dover's powder or .03 Gm. (½ grain) each opium and ipecac.

⁂ *Tinctura Opii Camphorata*, U.S.P. (Paregoric): 4 c.c. (1 drachm) = 0.016 Gm. (¼ grain) opium. This is the preparation of opium usually given to children in the following doses: For a child two days old, 2 drops; five days old, 5 drops; one week old, 6 drops; one year old, 10 drops; two years old, 12 drops; ten years old, one-half teaspoonful; adults, one teaspoonful.

For External Use:

⁂ *Lotio Opii et Plumbi*, N.F.: Lead acetate, 4.5 Gm.; *Tinct. opium*, 9 c.c.; water q. s. 250 c.c.

Liquid Opium Preparations of the British Pharmacopœia.

Extractum Opii Liquidum: contains 0.75% of morphin. *Dose:* 0.6 to 2 c.c. (10 to 30 minims).

⁂ *Tinctura Opii* (*Laudanum*): contains 0.75% of morphin. *Dose:* 0.6 to 2 c.c. (10 to 30 minims).

Tinct. Opii Ammoniata: contains 0.125% of morphin. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

⁂ *Tinct. Camphoræ Composita* (*Paregoric*): 1 fluidrachm = ¼ grain of opium. *Dose:* 2 to 8 c.c. (½ to 2 drachms).

Linimentum Opii: contains 0.375% of morphin.

The most important preparations are marked ⁂.

Morphina.—Prepared from opium. Soluble in 4350 parts water, 4000 ether, 400 alcohol; more freely in acetic ether or amyl alcohol.

Salts: ⁂ *M. Acetas* (U.S.P., B.P.).—Soluble in 2.5 water. (It loses in solubility on exposure.)
⁂ " *Hydrochloras* (U.S.P., B.P.).—Soluble in 24 water.
⁂ " *Sulphas* (U.S.P.).—Soluble in 21 water.
} *Dose*: 0.008 to 0.015 Gm. (1/8 to 1/4 gr.).
M. Tartras (B.P.).—Soluble in 11 water.

Preparations:

* *Hypodermic Solution*, N.F.—3.5%; 1 c.c. (15 minims) = .035 Gm. = 1/2 grain.

* *Syrupus Morphinæ Compositus*, N.F.—(For Cough.)

4 c.c. (1 drachm) =	Morphin sulphate	0.0022 Gm.	= 1/30 grain.
	Ipecac	0.008 "	= 1/8 "
	Senega	0.4 "	= 6 grains.
	Rhubarb	0.064 "	= 1 grain.

Morphin Preparations of the British Pharmacopœia.

	Strength per Cent.	Dose.	
		Metric.	Apothecaries'.
Liquor Morphinæ Acetatis, . . .	1	0.6 to 3 c.c.	10 to 50 min.
⁂ " " *Hydrochloridi*,	1	" "	" "
" " Tartratis, . .	1	" "	" "
Injectio Morphinæ Hypodermica, 1% of tartrate, ...		0.12 to 0.3 c.c.	2 to 5 min.
Suppositoria Morphinæ, each 1/4 grain, ...			
Trochiscus Morphinæ, each 1/36 grain,			
" " et Ipecacuanhæ, each 1/35 grain, ...			
Tinctura Chloroformi et Morphinæ Composita, ...	1	0.3 to 1.0 c.c.	5 to 15 min.

⁂ **Codeina** (U.S.P., B.P.).—Soluble in 80 parts water. *Dose:* 0.015 to 0.12 Gm. (1/4 to 2 grs.).

Codeinæ Phosphas (B.P.).—Sol. in 4 parts water. *Dose:* 0.015 to 0.12 Gm. (1/4 to 2 grs.).

Syrupus Codeinæ (B.P.).—1 fluidrachm = 1/4 grain codein phosphate. *Dose:* 2 to 8 c.c. (1/2 to 2 drachms).

* **Narcotin.**—*Dose:* 0.2 Gm. (3 grs.).

⁂ **Heroin.**—Soluble in water on the addition of a trace of acid (acetic). *Dose:* 0.005 to 0.01 Gm. (1/12 to 1/6 grain).

Sanguinaria (U.S.P.).—*Blood-root.*—The root of *S. canadensis*, Papaveraceæ. North America. Sanguinarin and other alkaloids of the protopin series; resins.

Preparations (not miscible with water):

Extractum S. Fluidum (U.S.P.).—Three-fourths alcohol. *Dose:* 0.06 to 0.3 c.c. (1 to 5 minims).

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* Not official.

The most important preparations are marked ⁂.

Tinctura S. (U.S.P.).—15%; two-thirds alcohol. *Dose:* 1 to 2 c.c. (15 to 30 minims).

Chelidonium (U.S.P.).—*Celandine.*—The root of *Chelidonium majus*, Papaveraceæ. Naturalized in North America. Alkaloids of the protopin series. *Dose:* 1 to 4 Gm. (15 to 60 grs.).

The fresh (red) juice is caustic and is used popularly to remove warts.

(B) CANNABIS INDICA AND SIMILAR DRUGS.

In this rather heterogeneous collection, a number of drugs have been placed, bearing a more or less close resemblance to morphin in their action upon the brain, but otherwise sufficiently different to prevent their being placed in the same or any other group; namely, Cannabis indica, Anhalonium and other cactus products, Lactucarium, and Lupulin.

They have no therapeutic importance. Since their action is largely a psychic one, which cannot be completely investigated on animals, they are very little understood.

Cannabis Indica.—This drug has, at least in this country, a theoretic rather than a practical importance. It is perhaps the most powerful stimulant of the psychic functions that we know, and is much used in the Orient for this purpose under various names, either the leaves of young twigs or the resin being employed. These are made into a confection or they are often smoked with tobacco. The effect is the same in any case. The user at first becomes very happy and hilarious. Everything amuses him. He also develops very affectionate tendencies, and thoroughly believes in universal brotherhood. Soon he becomes unconscious of his surroundings. His ideas scintillate, but he cannot fix his mind upon any subject. From this condition he gradually passes into melancholia and then into a deep sleep.

The intoxication differs from that of opium by the greater activity of movement and of imagination. The Oriental appears to be transported into his highest heaven and all that this implies. With Caucasians, the stimulating effect is smaller, but the intoxication is generally of a pleasant, jolly type. It may, however, be quite short and often absent, and is always followed by melancholia and sleep. On account of the latter, the drug has been recommended as a hypnotic. It is stated that it is not fatal even in very large doses, but experience on dogs certainly shows that it presents some danger. The habit to which it gives rise shows less effect upon the alimentary canal or marasmus than does morphin, but more often psychic alterations, dullness, or mania.

Therapeutically one can scarcely imagine any indication which might not be better and more safely fulfilled by other remedies.

One other hypnotic which may be discussed in this connection is lettuce juice, **lactucarium,** a remedy which has become practically obsolete, and has not been scientifically investigated. It is said that lettuce leaves also have some slight hypnotic power. The hypnotic action of **lupulin** or hops, which may be seen when they are administered in the form of beer, cannot be doubted, but it is certainly not very strong, and seems to be subject to considerable variations.

Jamaica dogwood (Piscidia erythrina, Papilionaceæ) is said to have an alkaloid, piscidin, with an action similar to hashish.

Related to the stimulating action of cannabis are certain products obtained by the Mexican Indians from the juices of various cacti, generally by fermentation. The most interesting of these is the **mescal,** prepared from Anhalonium Lewinii. This contains four alkaloids which agree qualitatively in their actions. The latter are quite numerous: a digitalis action on the heart, a curare action on striped muscles, a specific depression of the respiratory center, and a stimulation of other parts of the central nervous system. The stimulation is shown mainly in certain special senses, most conspicuously in vision, the effect appearing as a loss of coordination. It produces hallucination of all the special senses, but particularly of sight. There are flashes and lines of ever-changing colors. Since they are the same in both eyes, they must be central.

The drug is not at all used therapeutically, although the euthanasia which it produces even in small doses, and the digitalis action without a constriction of the vessels, might possibly be useful.

The Mexican drink "**pulque,**" produced by the fermentation of the juice of the maguey plant, produces an alcoholic intoxication modified by the presence of other substances, perhaps belonging to this group. In the intoxication, the thought and language are low, the patient is boisterous and quarrelsome, and, it is said, generally unhappy.

(C) HYDRASTIS.

The therapeutically active alkaloid, *hydrastin*, is closely allied chemically to narcotin:

$$C_{21}H_{20}NO_6.H = \text{Hydrastin.}$$
$$C_{21}H_{20}NO_6.OCH_3 = \text{Narcotin.}$$

In its action it follows *sanguinarin* in producing a *gradual central paralysis* in which narcosis is not especially prominent. It also *paralyzes the heart and skeletal muscles.* This is joined to a *strychnin action* on the medulla and spinal cord. As a part of this, it produces a great *rise of blood pressure*, and for this purpose it would be theoretically superior to strychnin, since this is among its first effects, and can be obtained almost pure.

The rise in blood pressure results not only from a stimulation of the vasomotor center, but also through *direct action on the muscles of the arterioles.* The latter effect, which is more marked in the artificial oxidation product hydrastinin, points to its use as a local hemostatic.

Small doses also seem to improve the action of the heart.

Therapeutically it has perhaps not been sufficiently tested to give a definite statement as to its value in collapse, etc.

On account of its vasoconstriction it is one of the best internal remedies against *hemorrhage* (see Chapter XXIII, A), and a local remedy against *catarrhal conditions* where a dilatation of the vessels exists. It would not be as useful as ergot against postpartum hemorrhage, since it does not cause contraction of the uterus. It would be more useful against profuse menstruation. In all these cases hydrastinin would be preferable.

Hydrastis has also been suggested as a measure against *epilepsy*, on the theory that it diminishes the activity of the motor areas, but this is not established.

Another hydrastis alkaloid, *canadin*, also has a morphin action, but it is present in too small an amount to be of any importance.

The third alkaloid, *berberin*, which is also found in berberis, calumba, podophyllum, etc., has practically no actions except those of a bitter substance.

MATERIA MEDICA.

Cannabis Indica (U.S.P., B.P.)—*Indian Hemp* (Hashish, Bhang, Ganja, Charas, Momeka, etc.).—The flowering tops of the female plant of *Cannabis sativa*, Urticaceæ. Collected in India.

Botanically, the plant is identical with that grown in the temperate zone, but the action is only developed in certain regions; in India itself only the plants growing above a level of 6000 to 8000 feet exude the resin "charas," which is considered the most valuable.

It was used in China as a medicine as early as the fifth century B. C., but the Greeks and Romans were probably not acquainted with it. It is now used as an intoxicant in many Eastern countries.

The plant has often been investigated with a view to isolating its active ingredients, but the results have been very unsatisfactory. The difficulty is enhanced by the extremely variable activity of the drug, which, furthermore, diminishes greatly on keeping. The activity seems to reside in the resinous substance.

Volatile oil, resins, cholin, (alkaloids?).

Preparations (alcoholic; not miscible with water):

Extractum Cannabis Indicæ (U.S.P., B.P.).—*Dose:* 0.015 to 0.03 Gm. (¼ to ½ grain).

Extractum Cannabis Fluidum (U.S.P.).—*Dose:* 0.06 to 0.6 c.c. (1 to 10 minims).

Tinctura Cannabis Indicæ, 15% (U.S.P., B.P.).—*Dose:* 1 to 2 c.c. (15 to 30 minims).

Cannabin, an alkaloid; *Cannabinol*, an oil; *Cannabinon*, a resin, are found on the market, and are claimed by their manufacturers to represent the active principles. They have not been subjected to sufficient scientific investigation.

Only such preparations should be employed as have been tested on dogs.

Lactucarium (U.S.P.).—*Lettuce-juice.*—The dried milky juice from the stalks of the Lettuce, *Lactuca virosa*, Compositæ. Cultivated.

Resin, gum; nature of active principle not determined.

Dose: 0.6 to 4 Gm. (10 to 60 grs.).

Preparations:

Syrupus Lactucarii (U.S.P.).—5%. *Dose:* 10 to 20 c.c. (2 to 4 drachms).

Tinctura Lactucarii (U.S.P.).—5%. Dil. alcohol and glycerin. *Dose:* 1 to 2 c.c. (15 to 30 minims).

Lettuce salad is also stated to have some hypnotic action with susceptible individuals.

Humulus (U.S.P.) [**Lupulus**, B.P.].—*Hops.*—The dried strobiles (female flowers) of *Humulus Lupulus*, Urticaceæ. Cultivated. The active part consists in small glands, which can be separated as a powder.

Lupulinum (U.S.P., B.P.).—*Lupulin.*—Volatile oil, cholin, resin; active principle not determined.

Dose: 0.2 to 1 Gm. (3 to 15 grs.).

Preparations:

Tinctura Humuli (U.S.P., B.P.).—20%; one-half alcohol. *Dose:* 8 to 30 c.c. (2 to 8 drachms).

Extractum Lupulini Fluidum (U.S.P.).—Alcohol (not miscible with water). *Dose:* 2 to 8 c.c. (½ to 2 drachms).

Oleoresina Lupulini (U.S.P.).—(Not miscible with water.) *Dose:* 0.3 to 2 c.c. (5 to 30 minims).

Infusum Lupuli (B.P.).—*Dose:* 30 to 60 c.c. (1 to 2 ozs.).

The hypnotic qualities of certain beers are probably largely due to their content of lupulin. The old beers were brewed without this addition. The first notice of such use occurs in 1050, but it was legally prohibited in England as late as 1530. At present the difficulty lies the other way, brewers sometimes adding other bitter substances—even strychnin and picrotoxin have been reported.

* **Piscidia.**—*Jamaica Dogwood.*—The bark of *Piscidia Erythrina*, Leguminosæ. West Indies. *Dose:* 1 to 3 Gm. (15 to 45 grs.).

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* Not official.

Hydrastis (U.S.P.) [**Hydrastis Rhizoma**, B.P.].—The rhizome and roots of *Hydrastis canadensis*, Ranunculaceæ. North America.

Berberin, 3 to 4%; hydrastin; canadin; resin.

Preparations:

⁂ *Extractum Hydrastis Fluidum* (U.S.P.) [*Liquidum*, B.P.].—Six-tenths alcohol, one-tenth glycerin. Miscible with water or alcohol. *Dose:* 2 to 8 c.c. (½ to 2 drachms).

⁂ *Glyceritum Hydrastis* (U.S.P.).—A fluid extract having equal volumes of glycerin and water as menstruum. Useful as injection. Miscible with water or alcohol. *Dose:* 2 to 8 c.c. (½ to 2 drachms).

Tinctura Hydrastis (U.S.P., B.P.).—20%; one-half alcohol. *Dose:* 8 to 20 c.c. (2 to 5 drachms).

* *Hydrastinæ Hydrochloras.*—Insoluble in water, readily soluble in alcohol. Not employed externally on account of its insolubility. *Dose:* 0.015 to 0.03 Gm. (¼ to ½ grain).

⁂ *Hydrastininæ Hydrochloras* (U.S.P.).—Prepared by the oxidation of hydrastin with nitric acid. Soluble in 0.3 water or 3 alcohol. *Dose:* 0.025 Gm. (⅜ grain). Hypodermically in 10% solution.

CHAPTER X.

COCAIN GROUP.

I. MEMBERS AND DERIVATION.

THIS comprises cocain and various alkaloidal and synthetic products of similar chemic composition. It also touches on several other groups which have the cocain action on the sensory nerve endings. The relation is also established through its chemic composition.

Cocain is very readily decomposed into benzoic acid and *ecgonin.*[1] The former may be replaced by other acids; the latter contains methyl, which may be replaced by other hydrocarbon radicles. It may be easily seen from this that through such changes artificial alkaloids can be formed; and similarly constituted alkaloids are found naturally in the leaves of coca, especially the Java variety. The structure of ecgonin is very closely related to tropin, the base of atropin.

Cocain is derived from the leaves of Erythroxylon coca, a tree indigenous to South America. The leaves were chewed from time immemorial by the natives to relieve fatigue and hunger, and also to produce psychic stimulation somewhat after the manner of caffein. It is now cultivated in some other tropical countries.

On the first introduction of the leaves into Europe the effects were disappointing, and the statements of the explorers were regarded as travelers' tales. These disappointing results were due to the fact that the sensations for which it is employed by the natives—hunger and fatigue—did not exist in the experimenters. The drug then fell very largely into disuse, since its anesthetic properties were not recognized. There is an isolated mention in 1860 that the chewing of the leaves paralyzes the sensation of the tongue, but it was only introduced into practice in 1884.

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[1] This occurs if solutions are heated for some time above 80° C. (176° F.). Cocain solutions cannot, therefore, be sterilized by boiling, but the object may be effected by bringing the solution repeatedly to 80° C. and cooling between.

* Not official.
The most important preparations are marked ⁂.

II. SUMMARY OF ACTIONS.

Cocain is a typical protoplasmic poison, and consequently produces the typical phenomena of death, consisting in stimulation with following paralysis of numerous structures, especially the following:

With *local administration* the endings of sensory nerves are paralyzed.

With *direct application* nerve trunks are paralyzed.

With *direct or systemic application* the pupil is dilated through stimulation of the sympathetic.

On *systemic administration* it causes an irregular, but on the whole a descending, stimulation and paralysis of the entire central nervous system.

Its protoplasmic action can be studied on lower organisms and on isolated cells. Through it, it is apt to produce local gangrene of the skin on hypodermic injection, and sometimes opacity and ulcers of the cornea when used in this situation.

While its toxic action is a general one and may be exerted on any protoplasm, yet it is relatively more marked upon nervous structures; and other tissues participate only under suitable conditions.

The order in which the *nervous structures* are affected depends upon the manner of introduction. On *systemic administration* it affects the central nervous system from above downward. The effect depends rather upon the dose than the time. The picture of the intoxication is quite complicated because, while one structure is already paralyzed, another is still being stimulated. In other words, there is a *simultaneous stimulation and depression of the different parts of the central nervous system.* Some portions of the nervous system appear to exhibit a stimulating action only, since the animal dies before the stimulation of these parts has worn off. This early death also explains why so little peripheral action is observed on systemic application.

When *locally* applied to the skin, it produces a paralyzing effect upon the peripheral nerve endings, and this without previous stimulation. The selective action is extremely marked in this case. Certain sensory nerves are especially liable, leading to the suppression of the sensation of pain and touch.

III. DETAILS OF ACTION.

Central Nervous System.—(*a*) The *frog* shows at first symptoms of stimulation by increase of the voluntary movements and exaggeration of the reflexes, sometimes leading to convulsions. This is followed by paralysis of the whole central nervous system.

(*b*) The symptoms in *mammals* resemble at once those of poisoning by atropin, morphin, and caffein.

(A) **Brain.**—The first effect is a well-marked stimulation of the higher parts of the brain (caffein action). This is shown in animals by increased movement, which is perfectly normal in character. In man there is a certain amount of *psychic stimulation* and also wakefulness. A greater *endurance against fatigue and hunger* is also noticed.

How far this may be due to a stimulation after the manner of caffein, or to a narcosis, after the manner of morphin, is impossible to state. It is not at all unlikely that both play a part. In regard to the sensation of hunger, it is also probable that local anesthetization of the stomach aids in the effect.

This stage of stimulation may be very short or even absent. With somewhat larger doses it may be followed by depression, first of the *coordinating functions*. The movements lose their purposive type and become choreic. There is then a general *narcosis* after the manner of morphin.

This is followed by *convulsions*.

The seat of these has not been exactly determined. They, like the other effects, are probably descending, and the different convulsive centers may be affected in succession. In some stages at least they seem to reside exclusively in the hind brain.

If the paralysis is rapid, the convulsive stages may not appear.

The *thermogenetic center* is stimulated, so that there is a rise of temperature.

(B) The **medulla** is affected at quite an early stage. The *respiration* is at first accelerated. During the spasms it is irregular. The volume then diminishes. It may assume the Cheyne-Stokes type. Respiratory paralysis is the usual *cause of death*.

This is also the first center to fail when the cocain is applied locally to the fourth ventricle.

The *vasomotor center* presents an early stimulation and much later paralysis. The changes in this center account for the variation in the quantity of urine, which may be increased, but is more often diminished.

The *circulation* is affected partly peripherally, partly centrally.

The effect will vary much according to the dose and also according to the individual. Different experimenters have, therefore, obtained different results. The following, however, appears to be the substance of the matter:

Pulse-rate.—1. *Diminished by very small doses*, due to stimulation of the vagus center. This is not seen, therefore, after section of the vagus trunk.

2. *Increased with moderate doses.* This is due mainly to the depression of the vagus center, but other factors must also be concerned, for some quickening occurs even when the vagus has been previously divided. In this case there must therefore be either a paralysis of tonic vagus ganglia or a stimulation of the accelerator mechanism.

The former, paralysis of the ganglia, occurs in the frog, and may be obtained in mammals on direct application, but not on injection, since the animals die before it can come to this action.

Since the *excised heart* (Hedbom-Langendorff) shows a lessening of both rate and systole, the quickening cannot be peripheral. It must, therefore, be accepted as due in part to the stimulation of the accelerator center.

The quickening in this stage is due, therefore, to depression of the vagus center and central stimulation of the accelerator.

3. *Slowed by large doses*, from depression of the cardiac muscles (since it occurs after atropin and is accompanied by weakening).

Pressure.—1. *Very small doses cause a notable increase* followed by return to normal. The depressing effect of the vagus stimulation is, therefore, overcome by the stimulation of the vasomotor center.

2. *Moderate doses cause, first, a temporary fall, then a very marked rise.* The fall may be considered due to the predominance of the slowing over the vasoconstriction. The rise is due mainly to the stimulation of the vasomotor

center, aided by the quickened heart. It is not due to convulsions, for it occurs in curarized animals.

3. *Large doses cause a very great fall*, due to depression of the heart muscles, and later of the vasomotor center (collapse).

The **vomiting** which frequently occurs in cocain-poisoning is perhaps due to the medullary stimulation, but its mechanism has not been fully investigated.

(C) **Spinal Cord.**—In frogs in which the brain has been removed, cocain causes at first an increase of the reflexes, then convulsions, and finally total paralysis. In intact animals this effect is obscured by the action on the higher centers of the nervous system.

THE LOCAL ACTION OF COCAIN.

(A) When cocain is brought into contact with the **nerve endings,** it paralyzes them in certain situations. In the skin it affects those having to do with pain and touch, but in a lesser degree or not at all, those having to do with temperature. In the nose it abolishes the sense of odor; in the tongue, the taste, especially for bitter, less for sweet and sour substances; it has no effect on salty taste.

It is absolutely essential that the cocain come into contact with the nerve endings or the nerve-fibers. This occurs sufficiently readily if the cocain solution is applied to the surface of the mucous membranes, but it cannot be absorbed in sufficient quantities from the unbroken skin. In this case it must be introduced subcutaneously. Since its action disappears very rapidly by its absorption into the circulation, the attempt must be made to limit it to the place where the action is desired.

Like quite a number of other poisons,—ether, alcohol, chloroform, carbolic acid, etc.,—it produces a *temporary paralysis of the nerve-trunk* to which it is directly applied. It lowers in this way all the functions of the nerve. It is possible to produce a *permanent* paralysis by application of a very strong solution. The sensory fibers of the nerves are paralyzed much more readily than the motor fibers, and the ganglia cells most readily of all.

When cocain is injected into the neighborhood of a nerve-trunk, it will only paralyze it if used in large amount. But if injected under the nerve-sheath, it produces a paralysis of the whole distribution of this nerve, which usually passes off after a time, without any bad effects. However, a strong solution may cause neuritis.

The production of wide-spread anesthesia by *injection of cocain into the spinal subdural canal*, which has been recently recommended, probably rests upon this same effect—*i. e.*, the lowering of the activity of the fibers of the nerve-roots. In this way a complete anesthesia to pain, less to touch, may be produced. The motor nerves are but slightly interfered with, while consciousness remains normal.

When cocain is applied to a mucous membrane, it renders it *anemic*. This is probably due to a local stimulating action on the arterial walls, although the cause is not certain. This effect, as well as the toxic action on protoplasm, produces an astringent sensation and an actual contraction of vascular formations, such as polypi.

In all these sensory effects there is no stimulation, such as would be evinced by pain, etc.

In man or the mammals cocain shows very little sensory effect when injected into the blood. This is due purely to its being fatal before the peripheral paralysis can make its appearance. The frog, which is much more resistant to the central action of cocain, can be anesthetized by its systemic application.

With the application of 2% to 10% solution to the mucous membranes, the anesthesia appears in a few minutes and lasts ten to thirty minutes.

Very large doses also paralyze the motor endings in frogs.

(B) Action of Cocain on the Eye.—When cocain is administered either locally to the eye or systemically, there is usually a submaximal dilatation of the pupil. The iris, however, still reacts to light. The accommodation is also impaired so that the punctum proximum is more distant.

The mydriasis differs from that produced by atropin, in the persistence of the reaction to light, and the dilatation is less complete. It also differs in several other respects: Pilocarpin and muscarin produce constriction easily after cocain, but not so readily after atropin. Cocain also produces a contraction of the vessels of the iris. The eyelids stand wide open: there is exophthalmos. The intraocular tension is reduced. These phenomena correspond exactly to those produced by the stimulation of the cervical sympathetic.

When the sympathetic fibers have degenerated (eight days after extirpation of the superior cervical ganglia) the cocain is inactive to the eye. Its effects must, therefore, be due to stimulation of the sympathetic, and since they do not disappear immediately after section of this nerve, but only after it has become degenerated, this stimulation must reside, at least in part, in the endings. But since it is then much weaker, it must be in part central.

The atropin dilatation is caused by paralysis of the oculomotor endings. This plays no part in the cocain action except with very strong solutions, for stimulation of the oculomotor trunk still causes contraction.

In birds' eyes cocain produces no dilatation, whereas in frogs it is very marked.

In addition to the mydriasis, it of course also produces anesthesia and destruction of reflexes, such as winking, when locally applied.

Cocain sometimes produces cloudiness and even gangrene of the cornea, due to its protoplasmic toxicity.

Cocain has practically no effect on **secretion**, nor has it any action on **metabolism** beyond the increase of temperature, which has already been noted.

In mice it causes a fatty infiltration and vacuolar degeneration of the liver-cells.

Very little is known about the **fate** of cocain in the organism.

IV. OTHER MEMBERS OF THE GROUP.

Eucain, α and β.—These are synthetic products which have, in general, the same action as cocain.

The *central nervous system* is at first stimulated, then paralyzed, the *stimulation predominating*. In toxic doses convulsions form a striking feature. Slowing of the heart through stimulation of the vagus center, and a large fall of blood pressure on account of the direct depression of the cardiac muscle, are conspicuous.

The *peripheral action* is in general *less strong* than that of cocain. The pupil and accommodation are not affected, nor do the mucous membranes show paling.

The anesthetic action is also somewhat weaker. In the α it is preceded by stimulation and pain. The β is therefore preferred.

The eucains are perhaps one-fifth as toxic as cocain. No fatal cases have been reported even when several grams were used. The solutions have the advantage over cocain that they are not destroyed by keeping or heating. The hydrochlorate is used in 1% to 3% solution—generally twice as strong as cocain. It may be substituted for it in all cases.

Tropa-cocain, which occurs naturally in Java coca leaves, and which can also be prepared synthetically, has been claimed by its investigators to possess several advantages over cocain. It is not as poisonous, and it is said to produce deeper and more lasting anesthesia, but it has not been sufficiently tried. It is used in the same strength as cocain. It does not cause dilatation of the pupil, opacity of the cornea, or vasoconstriction.

V. RELATION TO OTHER GROUPS.

The cocain group is related to:

1. *Protopin* by its action on the central nervous system and on the sensory nerves. Through this to—
2. *Morphin;* also by its narcotic action.
3. *Atropin,* through its physiologic action on the central nervous system, the pupils and the sensory nerves; chemically, through tropin and ecgonin.
4. *Carbolic acid group* by its action on the central nervous system, the local anesthesia, and the benzoic acid radicle.

VI. TOXICOLOGY.

This is of special importance in view of the absorption which often happens on its application, locally or by hypodermic injection. The symptoms are somewhat variable. There may be excitement followed by depression and melancholia, or the former may be absent. When the drug is taken by the mouth, there is often the sensation of pricking of the tongue, nausea, vomiting, abdominal pain, etc.

The pupils are dilated and the accommodation impaired. The heart is quickened and shows palpitation; the respiration is accelerated and deepened, and later shallow and irregular and then Cheyne-Stokes; the skin is pale and cyanotic and often exhibits the sensation of formication. There is a feeling of faintness, vertigo, flickering before the eyes, then coma. The reflexes are heightened and may pass into choreic movements or general convulsions. This is followed by collapse. The cause of death is respiratory failure. The postmortem appearances are those of asphyxia.

The *treatment* consists in evacuation of the stomach and chemic antidotes if the drug has been taken by the mouth; otherwise, of the collapse treatment: Strychnin, caffein, ammonium carbonate, sinapism to the chest and abdomen. The head should be lowered. During the convulsions, chloroform and artificial respiration. Amyl nitrite is recommended.

Chronic Cocain-poisoning.—The effects of the cocain habit are essentially the same as those of opiumism, except that the psychic functions are more affected. There are insomnia, hallucinations, apathy, and melancholia. In addition, it produces marked digestive disturbance, hunger alternating with thirst, and constipation. After this, marasmus, debility, emaciation, anemia, edema, and ascites.

On withdrawal it presents abstinence symptoms similar to those of morphin, but not quite so violent. Cocain was at one time used for breaking up the morphin habit, but it should not be thus employed, since it is itself more dangerous than the latter.

VII. THERAPEUTICS.

1. **Central Nervous System.**—As a brain stimulant, against fatigue, and as a general tonic, it has no advantages and many disadvantages as compared with other substances, especially caffein and strychnin.

2. Its main use is for the **production of local anesthesia.**[1] In this connection it must be remembered that cocain acts only when it comes into actual contact with the peripheral sensory endings, hence it produces no effect when applied to the intact skin. It can, however, be absorbed from mucous membranes. It must also be borne in mind that its action ceases with absorption, and that, therefore, the local circulation must be restricted as far as possible (application of a constricting rubber band). The cocain itself aids in this by diminishing the local circulation through the anemia which it produces. This action may be supported by the addition of suprarenal extract (6% solution of the dried gland). The cocain is used in strength from 2% to 20% according to the location. The anesthesia appears in about five minutes and lasts for about thirty minutes.

In *eye* and *larynx operations* the abolition of reflexes and the diminution of hemorrhage are very useful side-actions. In connection with its action on the eye, it must be remembered that it does not anesthetize the iris when applied to the cornea.

Cocain is also very useful in the treatment of diseases which appear to be due to heightened irritability of the peripheral endings, such as *hay-fever* and *asthma*. In these the cocainization of the nasal mucous membrane is often specific. The danger of the formation of the habit very often interferes with its use.

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[1] No method of local anesthesia can prevent the "psychic pain," the nervous dread of the patient, the removal of which is one of the most valuable features in narcosis. This object may be accomplished by giving ¼ grain (0.015 Gm.) morphin hypodermically fifteen to thirty minutes before the operation.

One per cent. cocain ointment has been recommended in herpes zoster; it is said to not only relieve the pain, but to put a stop to the disease.

The comparative value of cocain and its succedanea is discussed on pages 234 and 238 to 240.

When it is desired to do *larger operations* under the influence of cocain, it would seem best to use it according to the *method of Schleich.*

He uses very dilute solutions (1 : 10,000 to 1 : 500) at the very place where the incision is to be made and injects them in such quantity as to produce a local edema. This distention is in itself anesthetic, even when produced with pure water, by causing local anemia and compressing the nerve-filaments. The effect is the larger, the colder the solution. This edema is very painful unless produced by isotonic solutions. The ischemia is also useful in furnishing a bloodless field of operation. The injection may be made with an ordinary antitoxin syringe, but an injection apparatus is a great convenience. From 1 to 20 ounces of the solution are used, it being essential to produce *edema* of the whole field of operation.

Schleich begins by injecting the solution into (not under) the epidermis until it raises a blister; when this is anesthetized, he injects somewhat deeper, and so on until the whole field of operation has been covered. The use of long needles avoids too numerous punctures.

The solutions contain:

	I.	II.	III.
Cocain	0.2	0.1	0.01
Morphin	0.025	0.025	0.005
NaCl	0.2	0.2	0.2
5% Carbolic acid	5 drops per 100 c.c.	same	same
Aqua destillata ad	100	100	100

I is used when inflammation exists.

II is most generally useful.

III is employed where much solution is required.

The morphin in these might as well be omitted.

Another way of using cocain in extensive operations is to inject it into the *nerve-trunk* supplying the region (intraneural method). A 2% solution may be employed. While this method is frequently very successful, it has sometimes given rise to neuritis. The cocain may also be injected in the neighborhood of the nerve-trunk (paraneural method). All these may be usefully combined.

Another method which has recently been advanced is to inject the cocain directly into the spinal canal, where it probably acts in the same way as when injected into the nerve-trunk. This method has been favorably reported on, and seems to give good results in practiced hands. It produces complete anesthesia, slight diminution of motor power, and absolutely no effect upon consciousness. The anesthesia begins in from four to ten minutes, and lasts from one-half hour to two hours. About 15 mg. (not over 20 mg.) in 2% solution (½ to 1 c.c.) are injected between the second lumbar and the lumbosacral vertebræ by means of a long platinum needle. Some observers have also used this method in obstetrics and claim favorable results, although it might be supposed to lessen the contractions of the uterus. It can scarcely be supposed entirely free from danger, since the solution may spread up in the spinal canal to the medulla (Crile). The mortality is about 1%. The injection should be made as low as possible in the cord. Eucain has not been sufficiently tried, but seems to require much larger doses.

Cocain is also useful locally in *hemorrhoids*, producing contraction and diminishing pain. It has been taken by the stomach to prevent *vomiting* and dyspeptic pain.

A peculiar and unexplained fact is that cocain sometimes does not produce its characteristic action, especially when acute inflammation is present. This does not seem to depend on any chemic change in the solution.

3. **Side-actions.**—Besides the danger of the formation of the habit, there are several other objections to its use, consisting in acute poisoning and some side-effects. Very small doses sometimes produce fatal results. The smallest fatal quantity on record is 0.08 Gm. One Gm. altogether should never be exceeded, and 0.07 Gm. is the safe limit.

Among the side-effects, headache, insomnia, and vomiting are especially prominent.

VIII. OTHER DRUGS PRODUCING LOCAL ANESTHESIA.

Cocain and the alkaloids of its group are by no means the only substances capable of paralyzing the sensory endings. Any protoplasmic poisons may do so under proper conditions, but the side-action of many of these may prevent their practical employment. Others, again, do not produce complete anesthesia, but have considerable importance when a prolonged action with intact skin is required, as in neuralgic and rheumatic pains, bruises, etc.

1. *Atropin* somewhat resembles cocain in its action, but is not nearly so strong. On the other hand, it is more readily absorbed from the intact skin, and can be employed in liniments and plasters.

2. *Aconite* causes first irritation and then anesthesia of the sensory nerves without inflammation.

3. *Mechanical Means.*—(*a*) *Protracted tepid baths.* These are useful especially in inflammation and skin diseases.

(*b*) *Cold baths* or *freezing* produce, in addition, local anemia. The anesthesia in freezing is complete, but it has several disadvantages. It is preceded by violent pain, and is often followed by vesication and gangrene of the skin. The freezing may be done in emergency by the application of ice and salt mixture, but more conveniently by spraying the surface with an easily volatilizable substance such as ether, or especially ethyl chlorid.

4. *Counterirritants* all produce a depression of the nerves after their stimulation. Here belong menthol, camphor, turpentine, essential oils, chloroform, alcohol, etc. (See Chapter XXIX, E.)

5. Local anesthetic action is possessed by quite a number of the *aromatic series*. One of the most important is *carbolic acid*. This produces a marked anesthesia even in quite dilute solutions. Its application is, however, often injurious, since it produces destruction of the skin, and it may be absorbed in sufficient quantity to cause toxic symptoms. It is sometimes used in *paracentesis*, by applying a drop of the concentrated liquefied phenol to the skin, for the double purpose of anesthetizing and disinfecting. All the bodies of this series show both actions. Acetanilid or antipyrin may both be used in wounds in the form of dusting-powder, but are weaker.

The most useful drug of this kind is **orthoform.** This has the same pharmacologic action on the sensory nerves as cocain, but differs from it in being almost completely insoluble; and as it is also very rapidly excreted, it is practically non-toxic. This is quite an advantage when large open surfaces, such as ulcers, are to be kept under the continued influence of a local anesthetic.

On the other hand, its insolubility precludes its use in hypodermic injection. When it is artificially brought into solution and injected, it is no less dangerous than cocain and has no advantage. Like cocain, it does not penetrate the intact skin, nor even mucous membranes, so that its usefulness is limited to open surfaces. Here its action may be prolonged for days. It has, however, in some cases caused a necrosis. Another use has been to mix it with caustics to deaden the pain of the latter. It has also been employed internally in ulcers or carcinoma of the stomach.

Holocain is another coal-tar derivative which has been introduced as an anesthetic in ophthalmologic practice. It paralyzes the sensory nerves of the cornea even more powerfully than cocain, and does not produce any necrosis, so that it possesses some very marked advantages. No toxic symptoms have ever been observed, and solutions are not decomposed on boiling. However, it has no effect upon the pupils nor upon the blood-vessels, and this may make it undesirable in some cases. For the removal of foreign bodies one would prefer holocain, whereas for bloody operations, and especially for operations on the lens, the cocain would deserve the preference. In nasal operations the shrinking effect of cocain upon polypi may be a serious disadvantage in snaring, and holocain would be preferred.

It is used in 0.5% to 1% aqueous solution. The anesthesia appears in less than half a minute and lasts from five to ten minutes.

Chloroform-acetone (anesone; chloretone), used in a 2% solution, also has a local anesthetic action. It is inferior to cocain, but is somewhat antiseptic.

Nirvanin, another patented coal-tar derivative of the orthoform type, is soluble in water, can be sterilized, and is itself antiseptic. Used in 2% to 5% solution. Stated to be one-tenth as toxic as cocain and non-irritant.

Acoin, a guanidin derivative of anesthetic properties, used in ⅓ to 1% solution, is objectionable, since it is quite irritant.

IX. MATERIA MEDICA.

Coca (U.S.P., B.P.).—The leaves of *Erythroxylon Coca*, Lineæ. Peru and Bolivia, cultivated.

Cocain and similar alkaloids; tannin.

Preparations:

Extractum Cocæ Fluidum (U.S.P.) (*Liquidum*, B.P.).—*Dose:* 4 to 15 c.c. (1 to 4 drachms).

* *Vinum Erythroxyli* (*Cocæ*), N.F.—6½%. *Dose:* 30 to 60 c.c. (1 to 2 fl ℥).

* *Elixir Erythroxyli*, N.F.—12%. *Dose:* 30 c.c. (1 fl ℥).

* *Elixir Erythroxyli et Guaranæ*, N.F.—12% of each. *Dose:* same.

Cocaina (B.P.).

⁂ *Cocainæ Hydrochloras* (U.S.P.) [*Cocainæ Hydrochloridum*, B.P.].—Soluble in 0.5 part water. Solutions cannot be sterilized by heat and deteriorate on keeping. *Dose:* 0.008 to 0.12 Gm. (⅛ to 2 grs.). Hypodermically, in 1 to 2% sol. On mucous membranes, in 2 to 10% sol. Infiltration, see page 237. Intraspinal, 15 mg. in 2%.

Lamellæ Cocainæ (B.P.). Each 1/50 gr. of hydrochlorid.

Injectio Cocainæ Hypodermica (B.P.).—10%. *Dose:* 0.1 to 0.3 c.c. (2 to 5 minims).

Unguentum Cocainæ (B.P.).—4%.

* Not official.

The most important preparations are marked ⁂.

Trochisci Krameriæ et Cocainæ (B.P.).—Each $\frac{1}{20}$ grain.

⁂ *Eucain β.*—Artificial alkaloid. Soluble in water. Solutions can be heated and keep well. Used in 2% solution.

⁂ *Holocain Hydrochlorid.*—Phenacetin derivative. Soluble in 40 water. Used in 1% solution.

⁂ *Orthoform.*—Synthetic compound, but slightly soluble. Locally as dusting-powder or as 10 to 20% ointment.

X. DRUGS PARALYZING TASTE ORGANS.

Allied in this respect to cocain, there are a number of substances whose action is, however, confined to taste. (See p. 115.)

Gymnemic Acid (from *Gymnema sylvestris*).—Destroys bitter and sweet; not acid or salt.

Eriodictyon (U.S.P.).—*Yerba Santa.* The leaves of *E. glutinosum*, Hydrophyllaceæ. California. Destroys bitter taste; not sweet, or salt, acid.

Volatile oil, resin, glucosid, eriodictic acid, tannin.

Preparations:

Extractum Eriodictyon Fluidum (U.S.P.).—Alcohol four-fifths. Makes turbid mixture with water. *Dose:* 0.6 to 2 c.c. (10 to 30 minims).

⁂ *Elixir Eriodictyon Aromaticum*, N.F.—*Elixir Corrigens.* 6%. *Dose:* ad libitum.

CHAPTER XI.

(A) THE ACTION OF DRUGS UPON THE HEART.

Since many of the following drugs have some of their most characteristic and interesting actions upon the heart, and since this organ has an extremely complicated physiology, it will be well to devote a chapter to the discussion of the methods which can be used in studying this organ.

The physiology of the heart is a subject at present so much in dispute that almost every teacher and investigator favors a theory differing in more or less essential points from all others. The theories regarding the action of drugs upon the heart will, of course, vary as do those regarding its physiology. It is well, therefore, to recapitulate what is known with certainty, and to state further some hypotheses which will take account of the action of the different drugs. It must be clearly understood that these hypotheses are not stated as facts, but only as aids. Probably they will be shown eventually to be wrong in essential particulars.

I. INNERVATION OF THE HEART.

1. **Extrinsic Nerves.**—The heart is supplied by two sets of nerve-fibers, the *vagus* and *accelerator*. Stimulation of the former slows, of the latter quickens, the rate. The origin (center) for both of these nerves is in the medulla. Tonic impulses are continually passing down the vagus in certain mammals, particularly man and in dogs. There are no such tonic impulses to the vagus in some other animals:

The most important preparations are marked ⁂.

It is quite inactive in rabbits and has but a weak action in frogs. In those animals in which the vagus is tonically excited severance of these nerves will cause increased rate of the heart. Tonic impulses also seem to pass down the accelerator in like manner, but these have considerably less influence than those passing the vagus. The vagus fibers end in *ganglia* situated in the basal portion of the heart. These ganglia are connected by fibers and endings to the individual muscle-fibers. The *apex of the heart is free from ganglia,* but not from endings. The accelerator nerve also possesses ganglia, but these are situated outside the heart, the exact situation being unknown. They also end in the individual muscle-fibers. The nerve endings in the heart consist of "*free endings*" similar to those of unstriped muscles. There is no structure corresponding to the end plates of striped muscles.

There is a third set of extrinsic nerves in the heart; namely, *sensory.* These end free under the pericardium and endocardium, and are most numerous in the auricles. Their stimulation causes pain and a fall of blood pressure. Their fibers form the depressor nerve.

2. **Intrinsic Nerves.**—These consist of the *vagus ganglia* and both kinds of *fibers and endings.* The ganglia are most numerous at the junction of the auricles and ventricles. It must be considered as very doubtful whether any local reflex mechanism exists in the heart; *i. e.*, whether any impulses arising from one portion of the heart are transmitted to another portion by a nervous mechanism consisting of fibers and cells. The above-mentioned structures are, however, to a certain extent tonically active after severance of their central connections. They may be stimulated or depressed directly. They influence the rhythmic contraction and other phenomena of the heart. The influence of the central nervous system upon the heart is easily excluded by severance of the two vago-sympathetic nerves in the frog, or vagi and accelerators in mammals. When this is done, the heart still beats rhythmically and shows all of the typical phenomena. Since these phenomena may be seen on isolated apex preparations, it results that they can be produced by the muscle-fibers and nerve endings alone without the presence of nerve-cells. This does not, of course, show that the nerve-cells have no connection with the normal action.

II. PHENOMENA OF THE HEART.

So far we have been dealing with facts. We will now try to build up from these facts a theory to explain these phenomena.

1. **Rhythmic Beat.**—The power of rhythmic contraction may be considered as a property of the muscle-fiber, for which nervous structures are not necessary. They can, however, be modified by nervous impulses traveling down either the vagus or accelerator. Here, again, two different sets of effects may be produced; namely, upon the rate or the strength of the individual contractions. It is possible that these two sets of impulses pass along different nerve-fibers. The muscle is much less excitable to impulses setting up these rhythmic contractions in the absence of ganglionic connections.

We may consider that the muscle-fibers at the base of the heart are more subject to contraction than the apical fibers, and that on this account the contraction always normally starts at the base, and that the contraction wave started here is communicated by muscular conduction to the fibers toward the apex. When the excitability of the apex is increased, as by digitalis, independent contractions may take their origin here.

2. **The strength of the contraction** will depend largely upon the state of the muscle. It may be modified in the following ways: in rapidity; in greater capacity for relaxation (greater diastole); in an increased tendency to contraction (greater systole), which may find its expression in greater individual contractions, or in later stages leads to permanent contracture or increase in tone. Still more advanced action along this line would lead to systolic standstill. The coordination of the muscular contraction may also be influenced. It is conceivable that an increase of the excitability beyond certain limits will cause contractions to arise at points other than the base instead of simply being communicated from the latter. In this case contraction would be perfectly irregular, and would give us a condition similar to the fibrillar contraction of delirium cordis.

3. **The rate of the heart** will be dependent upon: 1. The state of the muscle, its excitability, and its power of contraction and relaxation. 2. Upon the nervous mechanism, stimulation, or depression of either vagus or accelerator in any part of their course; this, again, may be direct

or reflex. 3. The state of the muscle may also be affected indirectly through change in the circulation by drugs acting either directly upon the coronary vessels or indirectly through the general blood pressure, an increased action of the heart causing an increase of the coronary circulation. The coronary circulation is in turn influenced by the state of the heart muscle, it being lessened by the dilatation of the heart.

The drug acting locally upon the heart may, therefore, affect: the muscular fibers, the vagus ganglia or endings, the accelerator endings, or the coronary circulation.

4. The following results may be produced upon the:

(a) Rate of the Heart:

Slowing:		*Quickening:*
Stimulation	Vagus center " ganglia " endings	Depression
Depression	Accelerator center " endings	Stimulation
Stimulation or depression	Reflex of the centers	Stimulation or depression
Diminished excitability Diminished power Increased excursion Diminished conductivity	Heart muscle	Increased
Decrease	Coronary circulation	Increase

(b) Work of Heart:

Increased.		*Diminished.*
Increased	Rate	Diminished
"	Force of muscle	"

(c) Amplitude of Excursions:

The latter is increased through mild, diminished through strong, stimulation of:

Vagus mechanism: tends to diastole
Muscle-fiber: tends to systole.

4. By **local motor mechanism** is meant the power of *rhythmic* contraction possessed by cardiac muscle, as distinguished from its *individual* contractions. A muscle may have lost the former, but still possess the latter, although usually in weakened condition. As we have seen, this local mechanism is not *dependent* upon nervous connection, but is *influenced* by nerves, the latter probably modifying the muscle-fibers. We wish to lay particular stress that by

this term we do not mean any reflex chain consisting of afferent nerves, nerve-cells, efferent nerves, and ending-cells, but simply a physiologic peculiarity of the muscle-fibers, residing in the muscle-fibers alone.

Overstimulation of this mechanism at first causes the rhythmic contraction to become "*peristaltic*"—*i. e.*, a given plane being strongly contracted while a plane a very little below has not yet begun to contract. This peristalsis is followed in mammals, but not in frogs, by *fibrillary contraction* (delirium cordis), in which the contractions are without any order. This condition, again, is followed by paralysis. (The reason why frogs' hearts do not give this fibrillary contraction lies in the fact that the muscles in these animals are not so active; when their activity is raised,—*e. g.*, by heat,—they are also capable of fibrillation.)

5. **The tone, or elastic property,** of cardiac muscle means that functional state of the muscle by which it tends to assume a systolic condition. In light degrees, especially if the property of relaxation is at the same time heightened, this increases the efficiency of the contraction and the volume of blood thrown out, while a high degree of tone diminishes the efficiency by preventing the relaxation. If this property is still further heightened, it leads to systolic standstill, which persists in frogs, but is soon replaced by postmortem relaxation in mammals.

6. **Standstill** of the heart may be caused by excessive contractility of the muscle (systolic), or by the absence of this contraction—direct paralysis of the muscle (diastolic standstill). This, again, may involve only the power of rhythmic contraction, in which case stimulation of the heart, mechanically or chemically, will cause single contractions. Or the contractility of the heart may be abolished altogether. Or standstill may be caused by strong stimulations of the vagus in any part of its course. The seat of this stimulation can be shown to be above the ganglia by division of the nerve; at or below the ganglia, by drugs.

Standstill may also be brought about indirectly through insufficiency in the coronary circulation. If this is due to low blood pressure,—as, *e. g.*, in asphyxia,—the right side of the heart will be greatly distended, and when the blood pressure in the aorta is sufficiently diminished, the pressure in the right side of the heart may become greater than in the left, and, if this is the case, may establish a new coronary circulation in the reverse direction through the veins of Thebesius. This probably accounts for those cases in which the heart seems to recover spontaneously after once having stopped.

III. METHODS OF STUDYING THE HEART.

(**A**) The **influence of the central nervous system** may very easily be excluded by section of the nerve-trunks. Cyon has also devised a method of studying the effects of drugs upon the cerebral cardiac centers by separating these from the general circulation and artificially circulating through them defibrinated blood containing the poisons to be studied, which in this way do not reach the heart at all.

(**B**) The study of drugs upon the **peripheral mechanism** of the heart is complicated by the involvement of the general circulation. If it is desired to know with certainty the action on the heart, the latter must be completely isolated from the peripheral vessels. This is comparatively easy in the **frog**, and one of the neatest devices for this purpose is the Williams apparatus. Having ascertained the action of the drug upon the entire heart, it is necessary to locate its exact seat; whether this is in the ganglia, either kind of endings, or muscle-fibers. For this purpose we commonly make use of poisons, especially the following:

Nicotin to cause paralysis of the vagus ganglia.
Atropin to paralyze the vagus endings.
Muscarin or pilocarpin to stimulate the vagus endings.
Physostigmin or camphor to stimulate the muscle-fibers.
Apomorphin to paralyze the muscle-fibers.

It must not be thought that these poisons paralyze or stimulate exclusively those structures which are mentioned in this list. Their action is a much more extensive one, and they may even stimulate one structure while paralyzing another. However, when properly used, the above effects predominate so strongly that their actions may well be accepted in this sense.

(**C**) For the **isolation of the mammalian heart** various methods have been employed. It is necessary to study these in more detail, since in many cases the interpretation of the results will depend upon the method which has been employed.

The registration of the cardiac activity may be done by recording the contractions of the heart with a lever (myograph), or by measuring the blood pressure in the cavity of the heart, or by estimating the volume of blood which the heart throws out in a given time or at each contraction.

Methods for the study of the mammalian heart may be classified as follows :

I. Those using the **heart under nearly normal conditions.**

1. The method involving the least operative procedure is that of measuring the volume of the output of the heart according to the *method of Stewart.* The principle of this is to inject a known amount of dilute salt solution into the circulation. From the difference in the conductivity of a sample of defibrinated blood, before and after injection, the amount of salt solution with which it has been diluted can be calculated. The factors of peripheral resistance, central innervation, etc., are, of course, present.

2. *Cardiomyograms* may be taken after opening the chest under artificial respiration and attaching levers to the heart by means of hooks and strings, etc. (Modifications of the method of Roy and Adami.)

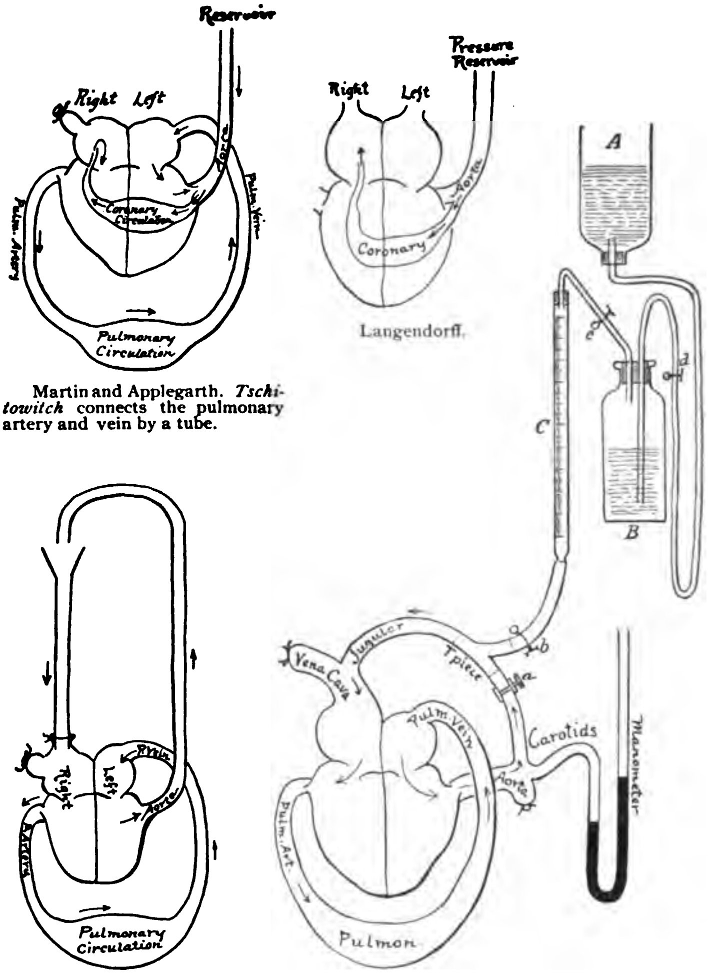
II. Methods employing the whole heart and pulmonary circulation (excluding the peripheral vessels and, to a large extent, the brain) (Fig. 48). These methods differ by the manner in which the action of the heart is observed or recorded, which may be done by direct observation, by taking pressure curves from the carotid or from the ventricles, or by the cardiomyogram. The methods rest essentially upon establishing a connection between the large arteries and large veins, and then ligating the vessels peripherally to this connection. The vessels which are employed for this purpose and the apparatus used for establishing the connections vary in the different methods :

(*a*) *Communication established between the aorta and right auricle :*

1. *Martin's original method.* In this, a communication is established through a reservoir containing defibrinated blood and connected with the right auricle, while the left ventricle pumps the blood through a tube back into the reservoir. The course of this blood then is : right auricle, pulmonary circulation, left heart, standing tube, and reservoir. The oxygenation of the blood is effected by artificial respiration.

2. *The modified method of Martin and Applegarth* establishes a communication through the coronary vessels, the

maintenance of pressure being aided by connection of the aorta with a reservoir containing defibrinated blood. The course of the blood is: aorta, coronary circulation, right heart, lungs, left heart, and aorta. Oxygenation is by artificial respiration.



Martin and Applegarth. *Tschitowitch* connects the pulmonary artery and vein by a tube.

Langendorff.

Martin's original method.

Bock.

Fig. 48.—Methods of studying the isolated mammalian heart.

3. *The McGrath and Kennedy method* is an amplification

of the last, in that it measures the intracardiac pressure and the outflow through the pulmonary artery.

4. *Hedon and Arrous' method* differs from the preceding methods by leaving out the reservoir, simply tying the aorta and its branches and the vena cava. The course of the blood is: aorta, coronary circulation, right heart, pulmonary circulation, left heart, and aorta. Oxygenation is by artificial respiration.

The heart survives some hours. It becomes progressively slower by the using up of material and the production of waste products, but it remains regular.

5. *Cyon* connects the aorta with the vena cava. In addition, he is very careful to ligate all the vessels leading to the brain, so that he can expose this organ to poisons without their reaching the general circulation.

(*b*) *Communication through the carotid and jugular.* The methods differ mainly in the mechanism introduced as resistance, this being either constant or variable:

1. *Stolnikow* makes the connection through two glass vessels of known content, which are reversible, and one of which is alternately filled by blood expelled from the heart, while the other empties into the vena cava. In this way the volume of blood expelled by the heart in a given time can be measured. The other vessels are, of course, ligated. Oxygenation is by artificial respiration.

2. *Bohr and Henriquez* establish the connection by a simple tube. *Hering* does not ligate the veins, using them as a pressure regulator. *Bock* forms the connection through a compressible tube and screw cock, so that a varying resistance may be introduced.

In all these methods the registration is done by a manometer in the other carotid, the aorta and vena cava being ligated and artificial respiration being kept up.

III. Completely isolated hearts; *i. e.*, without the pulmonary circulation, but with the ganglia still active. In these methods the blood must be artificially oxygenated, and is usually introduced under pressure. Otherwise the methods are similar to the preceding.

1. *Tschitowitch* uses practically Martin's original method, connecting the pulmonary artery with the pulmonary vein by a tube, the course of the blood being: reservoir, jugular vein, right heart, connecting piece, left heart, aorta, and reservoir.

2. *Langendorff* uses only the coronary circulation, introducing the blood into the aorta under pressure, from which it goes through the coronary circulation and flows out of the right heart. The shape of the heart, number and strength of beats, and the number of drops flowing through the right heart may be measured in this way.

A heart prepared in this way is subject to spontaneous changes, especially to gradual depression, and consequently conclusions on the actions of poisons can only be drawn: (*a*) if a change takes place, but disappears again when normal blood is circulated; (*b*) if a rather lasting acceleration occurs; (*c*) if the velocity of the coronary circulation is increased.

3. *Hedon and Arrous* ligate the aorta and vena cava and connect the pulmonary artery and pulmonary vein directly, feeding the heart with its own blood and keeping it alive by artificial methods.

IV. Isolated apex preparations; *i. e.*, ganglion-free heart muscle. *Porter* has succeeded in maintaining rhythmic contractions of isolated strips of the apex of the heart by injecting oxygenated blood under pressure into a branch of the coronary artery supplying it.

(B) ATROPIN GROUP.

This starts in a number of groups whose action is mainly peripheral, exerted upon ganglia and endings of glands, and cardiac and unstriped muscle. They also have an action upon the central nervous system.

I. MEMBERS.

The atropin group comprises a number of alkaloids of very similar composition: ether-like compounds (after the manner of cocain) of a base, *tropin* (or one very similar), and an acid. When obtained artificially, these are called *tropeins*.

The group includes:

Atropin:

Tropin and Tropic acid. $\left\{ (\underset{\text{Tropin}}{C_8H_{15}NO} + \underset{\text{Tropic Acid}}{C_9H_{10}O_3} = \underset{\text{Atropin}}{C_{17}H_{23}NO_3} + H_2O). \right.$

Daturin identical.

Hyoscyamin isomeric.

Hyoscin (Scopolamin) very similar.

Duboisin. Mixture of last two.

Tropeins proper: *Belladonnin* = Belladonnic Acid Tropin.
Benzoyl Tropein = Benzoic " "
Homatropin = Oxytoluic " "

Ptomatropin, an unisolated ptomain of spoiled meat, has apparently an identical action.

Derivation.—The different alkaloids are usually found in the same plants, and are formed from one another.

They are also formed in the process of extraction. The drugs which mainly contain them are:

Atropa Belladonna }
Datura Stramonium } Family of Solanaceæ.[1]
Hyoscyamus niger }

Others of much less practical importance are:

Duboisia myoporoides.
Mandragora autumnalis.
(Lactuca virosa?)

The first indubitable notice of belladonna occurs in 1504, but it then came quickly into use for poisoning and cosmetic purposes. The name Atropos is from the oldest of the Three Fates, who cuts the thread of life. Belladonna comes from the Italian, "handsome woman," as it was used to give luster to the eyes.

II. SUMMARY OF ACTIONS.

These differ only quantitatively in the different members of the group.

1. Excitation and then paralysis of certain parts of the central nervous system.
2. Primary paralysis of certain peripheral nerve organs.
3. Slight stimulation and subsequent paralysis of smooth and cardiac muscle.

The peripheral organs paralyzed are the nervous mechanisms of secretion, pupil and accommodation, and of unstriped muscle, especially intestinal and cardiac. In these respects it is the exact antagonist of muscarin.

On local application it paralyzes also the sensory nerve endings.

III. DETAILS OF ACTIONS.

1. Central Nervous System.—(A) **Hemispheres.**—These show exaltation, with a subsequent depression, especially of the psychic centers: Restlessness, vertigo, choreoid movements, incoherent and constant speaking, uncontrollable laughter, delirium, usually cheerful, and finally mania.

These actions somewhat resemble those of the excitement stage of alcohol, but from the general action of the poison, they are probably stimulant, whereas the latter (of alcohol) are depressant.

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[1] The family of Solanaceæ also contains Tobacco, Capsicum, Potato, etc.

In the secondary *paralytic stage*, drowsiness, coma, and finally convulsions occur, the latter largely from asphyxia.

Some other cerebral centers are also affected:

The *vision* is disturbed more than can be explained by loss of accommodation.

The *motor areas* in dogs are stated by some observers to be more excitable, but others deny this.

Hyoscyamin and hyoscin differ in so far from the typical atropin action that they produce sleep without primary exaltation. They are, however, somewhat uncertain as hypnotics.

Hyoscin, $\frac{1}{250}$ grain hypodermically, also often entirely arrests the tremors of paralysis agitans and of lead-poisoning.

(B) The effects on **medulla and spinal cord** are similar in kind to those of strychnin, but are weaker and come on much later in the course of the poisoning. They are therefore of comparatively little importance.

Paralysis of respiration (Fig. 49, *C*) is the usual *cause of death*, but comes on very late.

With atropin the affection spreads from the hemispheres downward. Caffein, atropin, and strychnin forming a regular series in this respect. Caffein acts most on the uppermost portion of the neural axis, strychnin on the lowest, and atropin stands intermediate.

2. **Peripheral Actions.**—(A) **Glands.**—One of the first symptoms of atropin-poisoning is dryness of the mouth, hoarseness, thirst, difficult articulation, and dysphagia, from the suppression of the secretions of the mouth. It diminishes not only the saliva, but also mucus, sweat, gastric (both quantity and acidity) and pancreatic juice, and milk. On urine it has but a small effect.

The *mechanism of this action* can be best studied on the *submaxillary gland*. One can at once exclude any central paralysis, for electric stimulation of the chorda tympani has no effect. The paralyzing action is therefore peripheral, and could be on the ganglia, endings, or salivary cells. The former are excluded by the fact that stimulation of the nerves peripheral to the ganglia is also ineffectual. Further, nicotin (which stimulates ganglia) does not act after atropin. We can eliminate paralysis of the gland-cells,[1] for stimulation of the sympathetic is still effectual. By exclusion, it results that the action must be on the nerve endings.

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[1] This is the theory generally held. Recent experiments go to show that atropin acts also on the cells, paralyzing the functions excited by the chorda, but not those under the control of the sympathetic.

The chorda, besides secretory, also contains vasodilator fibers. The latter are not paralyzed, and stimulation causes an increased venous outflow from the glands.

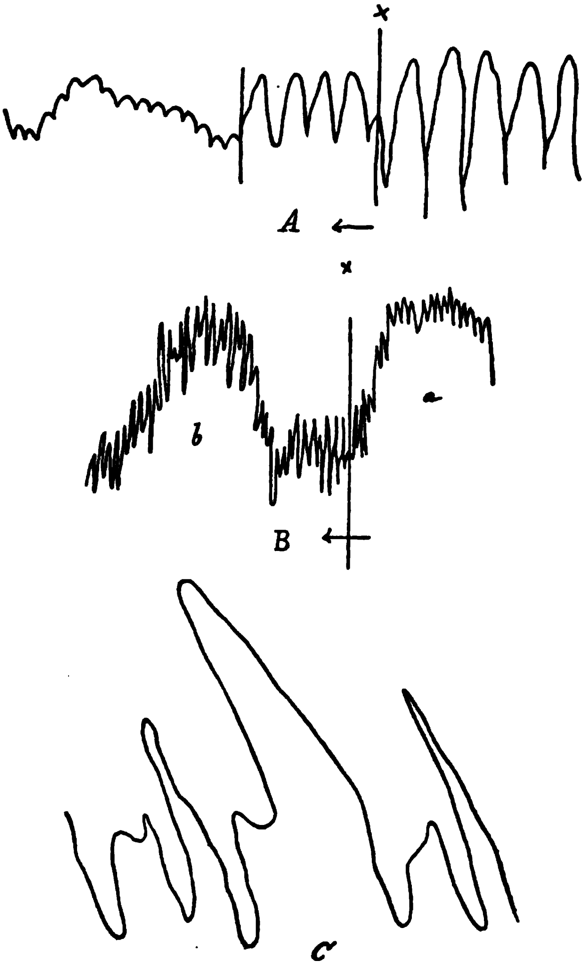


Fig. 49 —Atropin: action begins at ×. *A*, Carotid pressure, dog. Shows progressive quickening with smaller beats. *B*, Cardiomyogram, dog. The vagus ganglia were paralyzed by nicotin (*a*). The atropin causes strengthening of the beats. *C*, Cheyne-Stokes respiration after atropin (diaphragm-lever; dog).

The secretion of saliva being entirely dependent upon the integrity of the nervous connection, it may be entirely stopped by atropin. But with the other secretions the nervous influence is not so important, and hence they are not entirely arrested, although decreased. The point of attack is the same with them as with the salivary glands.

The nerve-fibers are not affected, even on direct application of the drug.

The nervous influences which cause the formation of sugar from glycogen in the liver are also cut off.

(**B**) In the **eye** atropin causes dilatation of the pupil and loss of reaction to light; loss of the power of accommodation; and rise of intraocular pressure.

(*a*) To explain this action, it will be well to recapitulate the anatomic basis of the *pupillary mechanism* (Fig. 50):

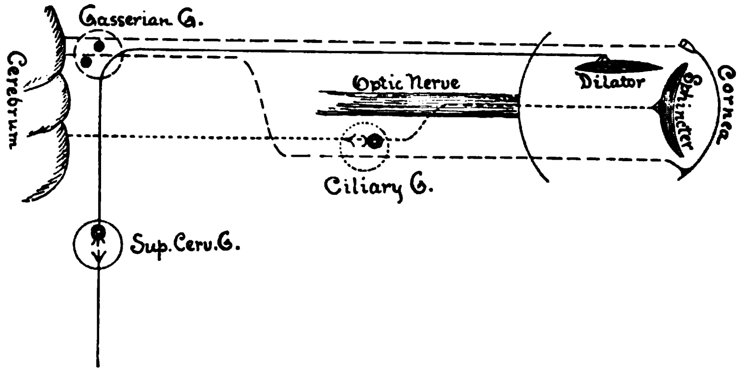


Fig. 50.—Innervation of pupil (adapted from P. Schultz): Solid line = sympathetic (dilator); fine dotted line = oculomotor (constrictor); coarse dotted line = trigeminal.

1. The pupil contains two sets of smooth muscle-fibers, the sphincters and dilators.

2. The former (sphincters) are innervated by fibers contained in the *oculomotor*. These terminate around the cells of the *ciliary ganglia*. From here the fibers pass as the *short ciliary nerve*.

3. The nerve-fibers for the dilators run in the *cervical sympathetic* and terminate in the *superior cervical ganglion*. The fibers which arise from here go direct to the dilator muscle without passing through any other cells. They run to the Gasserian ganglion, where they join the first branch of the trigeminal, and go from here as the *long ciliary* to the muscle.

The superior cervical ganglion also gives off fibers which go to the internal carotid, and, therefore, influence the blood supply of the eyeball.

The pupils may, therefore, be affected through the following mechanisms:

(A) DILATOR MECHANISM.	(B) CONSTRICTOR MECHANISM.
1. Sympathetic center.	7. Oculomotor center.
2. Sympathetic and long ciliary nerve.	8. Oculomotor and short ciliary nerves.
3. Superior cervical ganglion.	9. Ciliary ganglion.
4. Post-ganglionic fibers.	10. Post-ganglionic fibers.
5. Endings in radial muscle.	11. Endings in sphincter muscle.
6. Fibers of radial muscle.	12. Fibers of sphincter muscle.

Stimulation of "A" causes dilatation; paralysis, constriction through the unopposed action of constrictor mechanism.

Stimulation of "B" causes constriction; paralysis, dilatation through the unopposed action of the dilator mechanism.

Drugs do not act selectively upon the nerve-fibers.

Stimulation may be obtained electrically, paralysis by division. Either may occur through drugs.

(*b*) In the case of *atropin* it may be shown:

1. That the *action is local*, for:

(*a*) It remains confined to the eye, and even to that side of the eye to which it is applied.

(*b*) It can be produced on the excised eye of a frog and even on the isolated iris.

2. Of local mechanisms, we can at once *exclude direct paralysis of the muscle*, for these can be shown to be active by direct electric stimulation.

3. There remains only stimulation of the endings of the sympathetic, or paralysis of those of the motor oculi. The latter is the true explanation, for electric stimulation of the motor oculi is ineffective. Since stimulation of the ciliaris brevis is also ineffectual, the paralysis must be peripheral to the ganglion; *i. e.*, in the endings.

That there is, at the same time, a stimulation of the sympathetic is rendered improbable by the fact that atropin does not produce a stimulation of any other peripheral nerves, and a further dilatation may be obtained after atropin by stimulation of the sympathetic, electrically or by cocain (see p. 233). The absence of such stimulation by atropin is definitely proved by the following experiment:

If one superior cervical ganglion is excised in a cat and the fibers are allowed to degenerate, the corresponding pupil will, of course, be constricted on account of the unopposed action of the oculomotor. If atropin is now injected, it would cause a greater change in the healthy eye if it also stimulated the sympathetic. But this is not the case; the relative difference between the two eyes is preserved.

The dilatation is, of course, active, the contraction of the radial fibers being unopposed by the sphincter.

In birds, the iris is not affected by atropin, since it consists of striped muscle.

The statement that the muscular fibers are not affected by atropin must be limited to moderate doses. In greater concentration (according to most observers) it at first stimulates them, producing a temporary narrowing of the pupil; later it paralyzes them.

Direct application of very strong solutions to the ciliary ganglion also depresses this structure.

The *loss in power of accommodation* is also the effect of the oculomotor paralysis. *Increase of intraocular tension* usually accompanies dilatation of the pupil, however produced. The mechanism of this is still disputed. The most likely theory is that the muscular contractions occlude the efferent lymph-channels.

All these actions on the eye are produced on systemic as well as on local application. The mechanism is the same in both cases. On local application, atropin takes about one-half hour to fully dilate the pupil, and still longer to paralyze the accommodation; its action persists for some time, often several days. Even dilutions of 1 : 100,000 have some action, but the maximum is only reached with 1 : 100.

With homatropin the effects appear and disappear much more quickly; it is therefore better adapted for purposes of diagnosis, whereas atropin finds its proper use when it is wished to keep the pupil dilated for some time (iritis). Hyoscyamin and hyoscin are intermediate.

(C) The innervation of **smooth muscle** in other situations is paralyzed in the same manner as that of the sphincter of the iris.

1. Intestine.—Typical normal peristalsis, which depends upon the intactness of the peripheral reflex arch, is arrested; so is peristalsis caused by direct nerve stimulation (through muscarin, pilocarpin, or nicotin, or electric stimulation of the vagus). As moderate doses do not act directly upon the muscle-fibers, direct stimulation of these (or by physostigmin or some irritant cathartics) is still effective. Large doses also paralyze these, after previous stimulation. On account of the latter, peristalsis may be at first increased.

A precisely similar action occurs on that part of the *esophagus* which is composed of unstriped muscle.

2. On the smooth muscle of the *stomach, spleen, bladder, and uterus*, it acts only when they are tetanically contracted (as by muscarin or pilocarpin). Physostigmin is, of course, still active.

3. An exception to this nervous paralysis of unstriped muscle seems to exist in the case of *blood-vessels*, at least with moderate doses. In large doses it paralyzes these also, as can be shown by a larger outflow from isolated organs.

(**D**) Action on the **heart**: Atropin produces a paralysis of the vagus endings at or beyond the point where they are stimulated by muscarin. Stimulation of the vagus trunk or of the sinus therefore causes no slowing: it may, in the frog, produce an acceleration, since the accelerator fibers are not paralyzed by this drug. In animals in which the vagus is normally active (dog, and especially man) its paralysis will result in a greatly quickened heart-beat (in man there is a difference with age, the vagus being most active in middle life, less in old age, and least in infancy). In animals in which the vagus is not constantly acting (frog and rabbit) atropin will not change the rate. (Sodium iodid has a similar action on the vagus endings.)

Atropin has, in addition, a direct effect upon the heart muscle; it is stimulated by small doses (an exhausted apex preparation will beat again). Similar phenomena can be demonstrated on the isolated mammalian heart (Fig. 49, *B*). This action is, however, insignificant. In large doses the muscle is paralyzed, producing diastolic standstill.

It must not be forgotten that the cardiac centers in the medulla are also stimulated by the atropin. This is practically overshadowed by the peripheral action. But it may result in a primary slowing.

The action of the other members of the group upon the heart is very similar, belladonnin being the weakest.

(**E**) To sum up the action of atropin on the **circulation**, this shows a *quickening of the heart-beat* (Fig. 49, *A*) and a *rise in blood pressure*—the latter partly from the quickened heart, but largely due to stimulation of the vasomotor center (for it is much less after section of the cord). In fatal doses there is a great fall of pressure, due to paralysis of the vasomotor center and arterial muscles, and to paralysis of the cardiac muscle.

Another effect on the circulation consists in an intense *scarlet flushing of the skin*, particularly of the face and thorax; this is due to dilatation of the cutaneous vessels (vasodilator stimulation), with increased general blood pressure. This hyperemia may be so intense as to lead to desquamation.

(F) Of other peripheral actions, a *curare effect* on skeletal muscle endings in frogs (but not in mammals) may be noted.

The *sensory nerves* are dulled on local application, after the manner of cocain.

IV. TOXICOLOGY.

(A) Symptoms.—Atropin being absorbed very readily (and even from the intact skin), the *symptoms appear quickly*. The first to be noticed are those arising from *dryness of the mouth* and throat: difficulty of deglutition and articulation, great thirst, a sense of burning and constriction in the throat. On the eyes, the dilatation of the *pupils*, impaired vision, and absence of reaction to light will be noticed. There is often *nausea* and sometimes vomiting. *Excitement*, passing into delirium, is a prominent feature. The delirium is usually pleasing, with spectral illusions, but may become furious. The onset of the *paralytic symptoms* is ushered in by giddiness, numbness of the limbs, staggering gait, and passes into drowsiness and stupor. The *pulse* is quick and small. Scarlet flushing of the face. In *fatal cases* death is preceded by coldness of the extremities, rapid and intermittent pulse, and deep coma. Convulsions are rare.

The *postmortem* findings are those of asphyxia.

A fatal ending is, however, quite rare. Violent symptoms may last for days, and it has happened that patients have been consigned to the insane asylum on a mistaken diagnosis. The smallest recorded lethal dose is 120 mg. of atropin.

A psychic "slowness," disturbance of vision, and some other symptoms, may persist for weeks. On account of the slow course and the obscure symptoms, belladonna was a favorite with professional poisoners in the middle ages, and this abuse in regard to several species of Datura has existed in India since remote ages. The name itself is Sanskrit (Dhatoora).

(**B**) The **prognosis,** when properly diagnosed, is favorable, since there is ample time for interference. The **treatment** resolves itself into chemic neutralization, prompt removal, and meeting the symptoms. The delirium is best treated by the ice-cap, the general symptoms by pilocarpin (one-sixth grain hypodermically until mouth is moist). Morphin is also indicated in the early stages, but not after depression has set in. The latter is combated by the usual medullary stimulants (see p. 196). The effects on the eye may be abolished by the local application of physostigmin.

The **excretion** of the atropin occurs through the urine, for the most part in less than thirty-six hours; and the application of a drop of this fluid to the eye of a cat forms the most handy test for poisoning.

Atropin resists *putrefaction* for a long time, and may be found in the cadaver even months after burial. Confusion with ptomatropin must be guarded against.

Continued use of small doses seems to establish partial **immunity** to its action. It loses its effect first upon the salivary glands, then on the heart and intestine, and lastly on the eye.

Children bear proportionally larger doses than adults.

There also seems to be a sort of *racial immunity* to it. The suburban goat eats its thornapple weed with apparent relish, and seems none the worse for it, and rabbits have been fed on belladonna leaves so that their flesh proved poisonous to man, whilst they themselves showed no symptoms. Several generations have been raised of these animals, their food consisting exclusively of belladonna and stramonium leaves. This shows that whatever the cause, it cannot be ascribed to difference in absorption and excretion.

V. OTHER MEMBERS OF GROUP.

Of the other members of the group, the *differences* in their action have already been discussed. (Homatropin on the eye, p. 256; hyoscyamin and hyoscin on central nervous system, p. 252; belladonnin on heart, p. 257.)

The effect on the central nervous system may be arranged as:

Exciting action predominates:
↑ Atropin
Hyoscyamin
Hyoscin ↓
Depressing action predominates.

Relation to Other Groups.—*Cocain:* Constitution, effect on central nervous system and peripheral nerves.

Caffein and strychnin: Stimulating effect on central nervous system. The connection with *nicotin*, etc., groups will be discussed later.

VI. THERAPEUTIC USES.

(**A**) The effects of atropin on the **central nervous system** are sometimes used in *psychic depression*, especially in morphin-poisoning (p. 217), as also in mental disease. Since it does not act nearly so promptly or strongly as strychnin upon the medullary centers, it is of but little use in shock. The use of *hyoscyamin*, and especially *hyoscin*, as *hypnotics* and in tremors has already been discussed (p. 252).

As hypnotic sedatives, they are used in doses of 1 to 3 mg., especially in maniacal excitement and delirium tremens. In these conditions hyoscin must be preferred to morphin, since it lessens the motor disturbance, which is only increased by morphin, and it has the advantage over chloral of a slighter depression of the medullary centers.

Hyoscin has also been recommended for spasmodic affections, such as torticollis.

(**B**) Of the **peripheral actions**, those upon the eye are the only ones which can be obtained quite pure; but by carefully adjusting the dose, some of the other actions may also be utilized. The following *dosimetric table* (Schmiedeberg) will be found useful in this connection:

MG.	GR.	SYMPTOMS.
0.5 to 1	$\frac{1}{120}$ to $\frac{1}{60}$	Dryness in mouth, often with thirst.
2	$\frac{1}{30}$	Pupil dilated, not quite immobile. Increase of pulse-rate.
3 to 5	$\frac{1}{20}$ to $\frac{1}{12}$	Headache. Dysphagia. Alteration of voice. Muscular weakness. Restlessness.
7	$\frac{1}{9}$	Considerable dilatation of pupils. Disturbance of vision.
8	$\frac{1}{8}$	Excitement and muscular incoordination more marked.
10	$\frac{1}{6}$	Apathy. Unconsciousness. Hallucinations or delirium.

Except for use on the eye, it matters little which tropein is employed to secure a peripheral action; in practice, atropin is usually given the preference.

(**a**) **Eye:** mainly for dilating the pupil.

1. For *ophthalmologic examinations* the preference should be given to homatropin, since its effects set in and disappear

more quickly. It is used in 1 % to 2 % solution, dropped on the cornea.

2. In *iritis*, to secure rest, to prevent adhesions of the iris to the lens, or break them if already formed, and to effect assumed favorable changes in the circulation of the iris. The more prolonged action of atropin causes it to be preferred for this purpose.

Atropin is used in solution of 1 : 1000 to 1 : 100. Complete paralysis of accommodation is obtained in about an hour, and partially persists for several days. The dilatation of the pupils occurs much more promptly.

It must not be forgotten that these substances are harmful in glaucoma, as they increase the intraocular tension. They may also give rise to slight general symptoms (headache, dryness of mouth, palpitation).

(b) **Suppression of secretions**: against excessive saliva, sweat, milk, or bronchial mucus. As an *antisialogog* it may be useful in various intoxications (mercury, pilocarpin, etc.); as also in stomatitis. Atropin is, of course, purely symptomatic, and it is much more rational to remove the cause, which can usually be easily done. As an *anhydrotic* its principal use is in the night-sweats of *phthisis*, in doses of $\frac{1}{200}$ gr. Hyoscin may also be used. The allaying of the *cough*, by diminishing the secretion of mucus, is a useful effect in this as in other conditions. For this purpose, inhalation of atomized solutions is the best method of administration. A suppression of the hypersecretion of mucus also causes it to be employed in *bronchial pneumonia*, where it is also useful by stimulating the respiratory center.

(c) **Peristalsis**: Atropin may be used to stop a *diarrhea* which depends upon central influence, but is useless if the cause lies in the intestine itself. It will, on the other hand, be useful in constipation from tonic spasm of the intestine (*e. g.*, *lead colic*), just like morphin. It is frequently added to irritant *laxatives*, since, by preventing local contractions depending upon nervous stimulation, it obviates griping, and it does not, at the same time, interfere with the purgative action of the irritants (see Chapter XXX.) Preparations of the *crude drug* should be used for local action on the intestine.

The paralysis of unstriped muscle is also taken advantage of for the relief of *biliary and renal colic* from calculi. The vagus paralysis is also useful in this connection in preventing the dangerous slowing of the heart which sometimes occurs. *Incontinence of urine*, when due to overaction of the bladder muscle, is also relieved by it, as may also be retention of urine due to overaction of the sphincter. Its action on the *uterus* is entirely too uncertain to make it valuable in treating tetanic contraction of this organ.

(**d**) The **paralysis of the cardiac vagus endings** indicates it in all conditions in which slowing or even stoppage of the heart from stimulation of the inhibitory mechanism exists. This may occur in *pressure of the brain*. But it is a most frequent danger in the administration of *anesthetics*, especially of chloroform (see Chapter XIX, C). One-sixtieth of a grain hypodermically is the best way of obviating this accident, and the atropin is best combined with $\frac{1}{6}$ gr. of morphin (see p. 219).

(**e**) Another use of atropin is as a **local application**, usually in the form of liniment or plasters, for the *relief of pain*. The modus operandi has been discussed, but it is inferior in this respect to cocain, on the one hand, and counterirritants on the other (see Chapter XXIX). The antagonism of atropin and iodothyrin (see Chapter XIII) indicates it in Basedow's disease or thyroid poisoning.

We must, finally, mention the use of atropin, usually in the form of smoke from burning stramonium leaves, for the relief of **asthma.**

VII. THERAPEUTICS OF ASTHMA.

There are undoubtedly several varieties of asthma, requiring different treatment, but they all agree in some features, so that they can be classed together therapeutically as well as clinically. Many cases depend undoubtedly on reflex irritation, often from the nose (polypi, swelling of the turbinates, etc.). But it cannot be excluded that such reflexes may also arise elsewhere, especially from the walls of the bronchioles themselves. They lead to spasmodic narrowing of the lumen of the bronchioles by a hypersecretion of mucus, by congestion or swelling of the mucous membrane, or by tonic spasm of the bronchial musculature. Possibly all three of these factors may concur.

Considering the condition as a reflex, we may attack it therapeutically at the afferent or efferent end of the arch, or at the center. The first—the removal of the cause—is the most rational method. When gross changes, especially of the nose or pharynx, can be demonstrated, these should be removed. When the condition is one of increased susceptibility to unavoidable irritants (as to pollen in hay-fever), this may be lowered by cocain, or mechanical protection afforded by ointment. At the other end of the reflex arc a number of drugs meeting different indications may be employed.

1. *Iodids* act simply by rendering the secretion less tenacious, so that it may be expectorated. The same result could be reached by any other salt, and especially by alkalies, could they be brought to the site of the process; but with them this cannot be done nearly as efficiently as with iodids, since the latter are readily absorbed unchanged, and penetrate into all parts of the organism (Chap. XXV). The dose for this purpose is 1 to 3 Gm. (20 to 40 grs.) per day.

2. *Nitrites:* these, by lowering the general blood pressure, tend to diminish the congestion and secretion. Chartæ Potassii Nitratis act in the same way, and the empyreumatic products contained in the smoke act like the next group.

3. *Atropin* (stramonium; also lobelia, nicotin, and empyreumatic products in smoke): These act in several ways, by:

(*a*) relieving the muscular spasm through paralysis of the bronchial muscles;

(*b*) lessening the secretion;

(*c*) heightening the reflex activity of the respiratory center;

(*d*) conceivably also by diminishing the sensibility of the bronchial mucous membrane, when the beginning of the afferent path is situated here.

The usefulness of the different members of the series is not the same in all cases. This need scarcely cause surprise, considering the neurotic nature of the affection.

4. *Morphin* acts:

(*a*) by lessening secretion,

(*b*) by lessening of irritability of the center,

(*c*) by diminishing the discomfort of the patient.

Centrally we may achieve good results by two diametrically opposed sets of remedies:

1. By depressants, through

(*a*) lowering the reflex excitability of the centers concerned in the production of the attack.

(*b*) By narcotics, through diminishing the discomfort of the patient.

The same remedies meet indications *a* and *b*: Morphin, codein, alcohol, chloroform, KBr, HCN.

2. By stimulants, through increasing the activity of the respiratory center when it has become exhausted through the violence of the attack.

Among stimulants, caffein, strychnin, and atropin stand foremost for this purpose. The same result may be achieved through counterirritation (ammonia, sinapism).

Finally much of the discomfort of the patient may be removed symptomatically, by the inhalation of oxygen or compressed air (Chap. XX, B).

VIII. MATERIA MEDICA.

The materia medica of this group permits several **generalizations.**

The *percentage of alkaloids* is about 0.3; they always consist of a mixture.

The *Dose* of the *Fluid Extracts* = 0.06 to 0.2 c.c. (1 to 3 minims).

The *Dose* of the *Tinctures* = 0.3 to 1.3 c.c. (5 to 20 minims).

They are made with one-half alcohol and contain 15% of the drug. Miscible with water and alcohol.

The *dose* of the salts of the pure *alkaloids* = 0.0005 to 0.002 Gm. ($\frac{1}{120}$ to $\frac{1}{30}$ grain); *except* Hyoscin, 0.0004 to 0.0006 Gm. ($\frac{1}{150}$ to $\frac{1}{100}$ grain).

The salts are soluble in less than ½ part of water or 6 parts of alcohol.

Belladonnæ Folia (U.S.P., B.P.).—The leaves
Belladonnæ Radix (U.S.P., B.P.).—The roots
} of *Atropa Belladonna* (Deadly Nightshade), Solanaceæ, Europe and Asia Minor.

Constituents of Leaves: 0.35% of alkaloids, in which sometimes Atropin and sometimes Hyoscyamin predominate. Also small quantities of Belladonnin and other alkaloids. The *Root* contains 0.2% to 0.6% of the same alkaloids. The cortical portion is the richest. The young roots contain relatively more Hyoscyamin.

Preparations of the U.S.P.

Preparations from the Leaves:

Extractum Belladonnæ Foliorum Alcoholicum (U.S.P.).—*Dose:* 0.008 to 0.03 Gm. (⅛ to ½ grain).

Used in the preparation of:

Emplastrum Belladonnæ: 20% of the Extract.

Unguentum Belladonnæ: 10% of the Extract.

⁂ *Tinctura Belladonnæ Foliorum.*—15%. One-half alcohol. *Dose:* 0.3 to 2 c.c. (5 to 30 minims).

Preparations from the Root:

Extractum Belladonnæ Radicis Fluidum.—Four-fifths alcohol. *Dose:* 0.06 to 0.2 c.c. (1 to 3 minims).

⁂ *Linimentum Belladonnæ.*—Fluid Extract in which 5% of camphor is dissolved.

The most important preparations are marked ⁂.

Preparations of the British Pharmacopœia.

From the leaves:

Extractum Belladonnæ Viride.—Dose: 0.015 to 0.06 Gm. (¼ to 1 grain).

Succus Belladonnæ.—3% of the juice. *Dose:* 0.3 to 1.0 c.c. (5 to 15 minims).

From the root:

Extractum Belladonnæ Liquidum.—¾% of alkaloids. *Dose:* 0.03 to 0.06 c.c. (½ to 1 minim).

From this are prepared:

Extractum Belladonnæ Alcoholicum: By evaporation of the liquid extract with milk-sugar. Contains 1% of alkaloids. *Dose:* 0.015 to 0.06 Gm. (¼ to 1 grain).

Suppositoria Belladonnæ: Each contains $\frac{1}{60}$ gr. of alkaloids.

⁂ *Emplastrum Belladonnæ:* Contains 5% of alkaloids.

⁂ *Linimentum Belladonnæ:* Contains camphor.

⁂ *Tinctura Belladonnæ:* Contains 0.05% of alkaloids. *Dose:* 0.3 to 1.0 c.c. (5 to 15 minims).

Unguentum Belladonnæ: Contains 0.6% of alkaloids.

Stramonii Semen (U.S.P., B.P.).—The Seed }
⁂ **Stramonii Folia** (U.S.P., B.P.).—The Leaves } of *Datura Stramonium* (Thorn-apple, Jamestown Weed), Solanaceæ. Originally from Asia; naturalized in many countries.

The seed contains about 0.3%, the leaves 0.2% of alkaloids, mainly Atropin and Hyoscyamin. The latter predominates. The smoke of the burning leaves is inhaled for asthma. For this purpose they are best mixed with 10% of saltpeter.

The official *preparations* are made from the Seed.

Extractum Stramonii Seminis (U.S.B., B.P.).—Made with one-half alcohol. *Dose:* 0.015 to 0.03 Gm. (¼ to ½ grain).

Used in the preparation of:

Unguentum Stramonii (U.S.P.): 10% of the extract.

Tinctura Stramonii Seminis.—Made with one-half alcohol. (15%, U.S.P.; 20%, B.P.) *Dose:* 0.3 to 1.3 c.c. (5 to 20 minims).

Extractum Stramonii Seminis Fluidum (U.S.P.).—Made with three-fourths alcohol. *Dose:* 0.06 to 0.2 c.c. (5 to 30 minims).

Hyoscyamus [**Hyoscyami Folia**, B.P.].—*Henbane.*—The leaves and flowering tops of *Hyoscyamus Niger*, Solanaceæ; Europe and Asia. The plant should be of the second year's growth. Contains 0.3% of alkaloids, mainly Hyoscyamin and Hyoscin (the latter = Scopolamin).

Preparations:

Extractum Hyoscyami (U.S.P.).—Made with one-half alcohol. *Dose:* 0.03 to 0.1 Gm. (½ to 2 grains).

Extractum Hyoscyami Fluidum (U.S.P.).—Made with two-thirds alcohol. *Dose:* 0.3 to 1 c.c. (5 to 15 minims).

Tinctura Hyoscyami (U.S.P., B.P.).—Made with one-half alcohol. (15%, U.S.P.; 10%, B.P.). *Dose:* 1 to 4 c.c. (¼ to 1 drachm).

Extract. Hyoscyami Viride (B.P.).—A green extract. *Dose:* 0.1 to 0.5 Gm. (2 to 8 grains).

The most important preparations are marked ⁂.

Succus Hyoscyami (B.P.).—3% of juice. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

The *Seed* also contains the alkaloids. *Dose:* 0.1 to 0.3 Gm.

Alkaloids.

	Solubility in Water.	Solubility in Alcohol.	Dose.	As Mydriatic.
Atropina (U.S.P., B.P.) (from Belladonna) . . .	130	3.0	0.0005 to 0.002 Gm. ($\frac{1}{120}$ to $\frac{1}{30}$ grain).	
⁂ **Atropinæ Sulphas** (U.S.P., B.P.)	0.4	6.2	0.0005 to 0.002 Gm. ($\frac{1}{120}$ to $\frac{1}{30}$ grain).	1%
* **Daturin** = Mixture of Atropin and Hyoscyamin.				
* **Duboisin** = Hyoscyamin.				
⁂ **Homatropinæ Hydrobromidum** (B.P.) .	10	133	0.0005 to 0.002 Gm. ($\frac{1}{120}$ to $\frac{1}{30}$ grain).	1%
Hyoscyaminæ Sulphas (U.S.P., B.P.)	0.5	2.5	0.0005 to 0.002 Gm. ($\frac{1}{120}$ to $\frac{1}{30}$ grain).	
Hyoscyaminæ Hydrobromas (U.S.P.) . . .	0.3	2.0	0.0005 to 0.002 Gm. ($\frac{1}{120}$ to $\frac{1}{30}$ grain).	
⁂ **Hyoscinæ Hydrobromas** (U.S.P.)	1.9	13.0	0.0003 to 0.0006 Gm. ($\frac{1}{200}$ to $\frac{1}{100}$ grain).	
* **Scopolamin** = Hyoscin.				

B.P. Preparations of the Alkaloids:

Unguentum Atropinæ: 4%.
Liquor Atropinæ: 1%. *Dose:* 0.03 to 0.06 c.c. (½ to 1 minim).
Lamellæ Atropinæ: $\frac{1}{5000}$ grain each.
Lamellæ Homatropinæ: $\frac{1}{100}$ grain each.

* Not official.
The most important preparations are marked ⁂.

CHAPTER XII.

MUSCARIN-NICOTIN-CURARE SERIES.

(A) MUSCARIN GROUP.

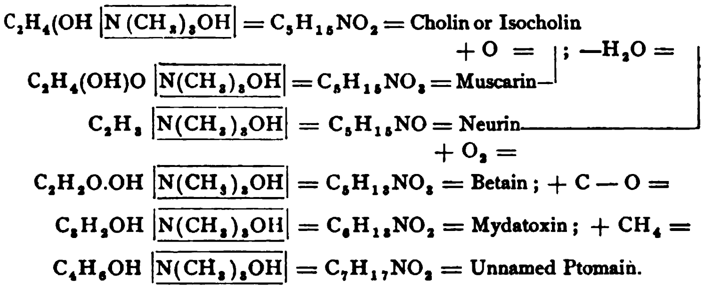
I. STRUCTURE, DERIVATION, AND OCCURRENCE.

THIS contains certain oxethylene-ammoniums. Their structure may be derived from Alcohol and Ammonium, as follows:

$$\begin{array}{ll|ll} C_2H_5(OH) & = \text{Alcohol} & NH_4(OH) & = \text{Ammonium Hydrate} \\ C_2H_4(OH)_2 & = \text{Glycol} & NH(CH_3)_3OH & = \text{Trimethyl-ammonium} \end{array}$$

$$C_2H_4OH\ \boxed{OH + H}\ N(CH_3)_3OH = H_2O + C_2H_4OH\ \boxed{N(CH_3)_3OH} = \underset{\text{Cholin.}}{}$$

The other members are derived from Cholin, as follows:



$$\begin{array}{rl} C_2H_4(OH\ \boxed{N(CH_3)_3OH} & = C_5H_{15}NO_2 = \text{Cholin or Isocholin} \\ & \qquad + O = \ ;\ -H_2O = \\ C_2H_4(OH)O\ \boxed{N(CH_3)_3OH} & = C_5H_{15}NO_3 = \text{Muscarin} \\ C_2H_3\ \boxed{N(CH_3)_3OH} & = C_5H_{15}NO = \text{Neurin} \\ & \qquad + O_2 = \\ C_2H_2O.OH\ \boxed{N(CH_3)_3OH} & = C_5H_{13}NO_3 = \text{Betain};\ + C - O = \\ C_3H_2OH\ \boxed{N(CH_3)_3OH} & = C_6H_{13}NO_2 = \text{Mydatoxin};\ + CH_4 = \\ C_4H_6OH\ \boxed{N(CH_3)_3OH} & = C_7H_{17}NO_2 = \text{Unnamed Ptomain.} \end{array}$$

This series might be still further extended. These substances are all formed in the putrefaction of nitrogenous matter, by the action of bacteria. They are, indeed, among the principal members of the group of "putrefactive alkaloids" or "*ptomains.*" But they are also formed in living plants, and especially in fungi. Muscarin, the typical member of the group, is contained in the fly-agaric, Agaricus (Amanita) muscarius, growing in birch and pine woods in many parts of the globe. It probably occurs also in some of the other poisonous fungi, but this has not been sufficiently investigated; one of the characteristic features of the members of this group—and of ptomains generally—is the ease with which they are decomposed, and this renders their investigation very difficult. One of the decomposition products of muscarin—and also of pilocarpin—has an atropin action, so that many samples are entirely worthless.

II. SUMMARY OF ACTIONS.

1. Stimulation of precisely those peripheral structures which are paralyzed by atropin. This stimulation is peculiar in not being followed by depression.
2. Affections of the central nervous system, as yet imperfectly studied.

3. A curare effect on motor endings, very inconspicuous in the case of muscarin itself.

There is no effect upon ganglia or nerve-fibers, even when the drugs are directly applied.

III. DETAILS OF ACTION.

1. **Heart.**—Muscarin causes *slowing* and stoppage in diastole, just as in electric vagus stimulation. The effect is more persistent than with the latter. This standstill occurs also in the isolated apex, showing that the stimulation is peripheral to the ganglia; and since it can be abolished by atropin or sodium iodid, the action cannot be on the muscle. It is therefore assumed that it stimulates those endings which atropin paralyzes. If muscarin and atropin are exhibited at the same time or successively, their respective quantity will determine which predominates. Drugs which act upon the ganglia—*e. g.*, nicotin—will be ineffectual; but the standstill may be raised by substances effecting a direct stimulation of the muscle-fibers—*e. g.*, physostigmin, veratrin, digitalin, anilin, camphor, guanidin.

The same stimulation of the vagus endings can be obtained by *iodothyrin*.

It is interesting that muscarin causes an acceleration of the crab's heart, although a well-defined inhibitory mechanism exists in these animals. The explanation undoubtedly lies in some structural peculiarity.

2. The effects upon the **eye** (exclusive stimulation of oculomotor endings), **glands, and unstriped muscle** in general are precisely the same as with pilocarpin. As to the *intestine*, small doses cause a stimulation of Auerbach's plexus: strong contraction and paling of the whole intestine. This is inhibited by atropin and by extremely large doses of the muscarin itself.

The muscarin group has only a scientific and *toxicologic importance*. Poisoning by mushrooms and meat is largely due to these substances.

(B) MUSHROOM-POISONING.

This topic still requires much elucidation. Undoubtedly different, although related, active substances are present in the various mushrooms as well as in different samples of spoiled meat.

The **symptoms** are accordingly quite variable. Features which are more or less common to mushroom-poisoning are: Abdominal pain, nausea, vomiting, and violent diarrhea; pulse variable; respiration labored; consciousness unaffected, or delirium; coma or convulsions. Some cause fatty degeneration of liver and kidneys. Many mushrooms produce abdominal symptoms simply by being indigestible.

Poisoning by the fly-mushroom, which has been best studied, presents a close resemblance to that by pilocarpin. The pulse is always slowed, and the blood pressure falls, as also through vasomotor paralysis. Muscular weakness and incoordination are among the more prominent symptoms. Death usually occurs after several days, the cause being yet obscure, but probably residing in the central nervous system.

The **treatment,** besides removal and chemic and symptomatic antidotes, as with pilocarpin, would be by atropin. The chance of poisoning may be somewhat diminished by prolonged boiling, as some of these substances are decomposed in this manner. This does not hold for the Amanitæ.

The proof of the poison consists in the demonstration of the physiologic action of the alkaline ether extract.

There seems to be an acquired immunity to the peripheral action of muscarin, as there is to nicotin and atropin: In Kamschatka the fly-agaric is used as an intoxicant, producing symptoms similar to those of alcohol, seemingly without exhibiting its peripheral action.

(C) CHOLIN, NEURIN, ETC.

These have some little importance as products of putrefaction, forming some of the poisonous ptomains. They are also formed during intestinal putrefaction, and may be absorbed in obstinate constipation in sufficient amount to produce symptoms. They also form the main active substances in extracts of nervous matter. Neurin is much more toxic than cholin. It may be formed from the latter by bacteria.

1. **The peripheral effects** agree with muscarin:

The peristalsis is increased (especially important when formed in the intestine, constituting a kind of natural treatment).

The heart is slowed (stimulation of the vagus).

The glands are stimulated (except bile).

Curare action. (This is quite strong, especially in cholin.)

2. They show some differences from muscarin in their **central action:**

They have only a feeble effect on the *brain* and *spinal cord;* considerable on the *medulla.*

The respiration is weakened through depression of the center.

The vasomotor center is first strongly stimulated, then depressed.

The blood pressure follows the vasomotor and cardiac changes.

(D) MEAT-POISONING.

The cases of poisoning observed as a result of partaking of more or less tainted articles of food—sausages (botulismus and allantiasis), meat, milk, ice-cream, cheese, corned beef, etc., and with some specimens of mussels and oysters—are due to the development of ptomain products. In the former cases these are developed by putrefaction; in the latter, probably by disease.

These ptomains have, for the most part, been isolated in crystalline form, and are perfectly typical compounds belonging to the amin series. Their pharmacologic action lies between that of atropin and muscarin.

The **symptoms** may be summarized as follows:

(a) *Gastro-intestinal disturbance:* nausea and vomiting, and either diarrhea or constipation. This is due to the local irritation, and, in addition, to stimulation or paralysis of the local nervous mechanism, and probably to some extent is central.

(b) *Dryness of mouth:* difficulty in swallowing, articulation, etc.; due to paralysis of the nervous mechanism of the salivary and mucous glands.

(c) *Pupil:* dilated by almost all; through an atropin action.

(d) *Heart:* quickened by atropin action.

(e) *Muscular weakness:* partly central; partly, and perhaps mainly, peripheral.

(f) *Sensory:* disturbed sensations of various kinds, formication, heat, etc.; probably central.

(g) *Medullary centers:* depression of respiratory and vasomotor centers, sometimes preceded by stimulation. The vessels of the skin are usually dilated, producing sweating, itching, heat, and erythema.

(h) *Brain:* the consciousness is usually not affected, but there may be delirium and later coma. When convulsions are observed, they are probably always asphyxial.

The perfectly fresh flesh of certain tropic and Russian fishes also produces central symptoms (Signatéra).

Tainted meat is also counted among the causes of scurvy.

The **treatment** in all cases would be mainly symptomatic, and no general rules can be given. Emetics and cathartics should be employed whenever necessary.

(E) PILOCARPIN GROUP.

This may be taken as representative of a series of groups (including nicotin, coniin, curarin, lobelin, gelseminin, and spartein), which all stimulate peripheral nervous mechanisms in those tissues in which they are paralyzed by atropin.

It comprises *pilocarpin* and *pilocarpidin*, from jaborandi leaves, and *nigellin*, from Nigella sativa. Only the former is of practical importance.

I. SUMMARY OF ACTIONS.

1. Stimulation, followed in larger doses by depression, of the ganglia and endings in precisely the same structures in which they are paralyzed by atropin.

2. A late and weak stimulation, followed by more conspicuous paralysis, of certain parts of the central nervous system.

II. ACTIONS IN DETAIL.

(A) Glands.—There is an increase in the secretion of saliva, sweat, tears, mucus, and of the gastric, pancreatic, and possibly of the intestinal juice.

The effect upon the secretion of milk is doubtful.[1] An increase in the proportion of sugar in the blood has been ascribed to the stimulation of the glycogenic nerves in liver. The secretion of urine and bile is not directly affected.

The general increase in the secretions is due mainly to water; but the total solids are also increased, although their percentage is lessened. The amount of water lost in this manner is very large—as much as a gallon after a single injection.

The *seat of the stimulation* is in the nerve endings or ganglia.

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[1] There are at present no really reliable data concerning the action of drugs (except alcohol) upon milk secretion.

It is not central, since it occurs after section of the nerves; nor does it reside in the cells, since it is stopped by atropin, which acts upon the nervous structures only. That it may occur through stimulation of the nerve endings is shown by the fact that in the dog's paw the secretion of sweat is increased by pilocarpin (after division of the sciatic), yet the sweat nerves in this situation possess no ganglia. But that it depends partly also upon stimulation of the ganglia is rendered very probable on account of its action on the heart, where, as we shall see, it stimulates these mainly; and, further, the dose of pilocarpin required to produce secretion after atropin is relatively much larger than that of muscarin (which stimulates the endings), showing that part of its action must be higher up than with the latter.

The antagonism to atropin is complete with both glands and muscles. When the two poisons are administered together, it is purely a question of the relative quantity of each substance present, as to whether increase or decrease of function will take place.

Acceleration of the blood current through the glands occurs as a secondary effect of their increased action. A common effect of pilocarpin, a hyperemia of the skin (resulting in an increase of its temperature), may possibly be due to the increased activity of the sweat-glands.

(B) **Unstriped muscle** generally (except that of blood-vessels, which appears exempt from its action) is thrown into contraction by stimulation of its peripheral nervous apparatus. This is most conspicuous in the *intestine*, resulting in increased peristalsis (diarrhea and colic). It occurs independently of the central nervous system, and is abolished by atropin in the same manner as the secretions. After very large doses, the stimulation is followed by paralysis. An identical action upon the stomach results in nausea, retching, and vomiting, but the effects upon this organ are much less than those upon the intestine. Of other unstriped muscle, that of the *bronchi, bladder, spleen, and possibly of the uterus*, is affected in the same manner.

(C) In the **eye** pilocarpin produces miosis and spasm of accommodation through stimulation of the motor-oculi endings and ganglia, the evidence being the same as in the case of glands. The intraocular tension is at first raised, followed by a more persistent fall, due to the miosis. Large doses produce late paralysis of the oculomotor endings, as elsewhere.

(D) In **frog's heart** it produces stimulation of the vagus ganglia with following paralysis. There is at first diastolic standstill, after which the heart returns to its normal rate. Stimulation of the vagus trunk is now ineffective, but stimulation of the sinus produces stoppage. This shows that the endings are not paralyzed, and the paralysis must therefore be limited mainly to the ganglia; although most observers also claim some affection of the endings in addition.

Very large doses again stop the heart, but since atropin does not remove this final standstill, it is evident that it must be due to direct paralysis of the heart-muscle.

In the *excised mammalian heart* (Hedbom-Langendorff) the action is the same, but the stage of vagus stimulation is short: The rate is suddenly slowed; this lasts but a short time; then there is marked quickening with increased tonus (paralysis of vagus). Large doses paralyze the muscle.

In those mammals in which the *vagus is constantly acting* —*e. g.*, dog and man—pilocarpin gives a marked acceleration of the pulse, with increased blood-pressure (Fig. 51, *B*) and later with arhythmia. The cause for this must be sought in vagus-paralysis; but the rise of blood-pressure is partly due to a stimulation of the vasomotor centers. In large doses this action is followed by muscular slowing and weakening of the heart, and consequently fall of pressure. This action, as in the frog's, cannot be removed by atropin, and is on the muscle directly. In rabbits, a primary vagus *stimulation* precedes the phenomena described for dogs, and makes itself felt by slowing of the heart and fall of blood-pressure; this action sometimes occurs in man and dog (Fig. 51, *A*).

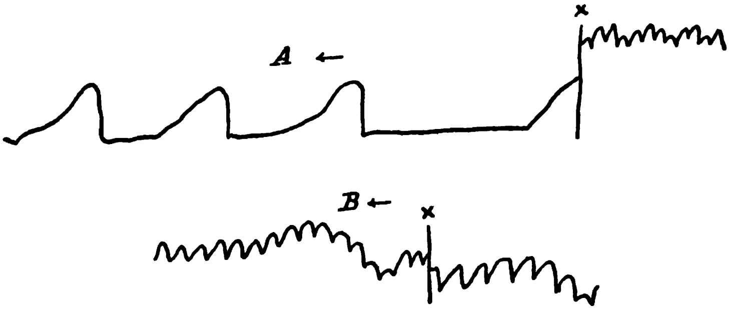

Fig. 51.—Pilocarpin. Carotid pressure, dog. The action begins at ×. *A* shows stimulation of vagus; *B*, depression of vagus.

(E) Central Nervous System.—The action is weak and appears late, so that it is entirely overshadowed by the peripheral actions. The effects are mainly *depressing* (and this applies to the other groups of this series). *Vasomotor paralysis* is a rather early and prominent symptom; it leads to *dyspnea.* Later, the *respiratory center* is also depressed. *Edema of the lungs,*[1] consequent on the weakened heart and obstruction of the bronchi by mucus, is a frequent occurrence. The *motor centers,* especially those of the cord, show some stimulation (increased reflexes, tremors, convulsions) and later paralysis.

III. TOXICOLOGY.

The toxicology of pilocarpin is not very important. The **symptoms,** which apply also to muscarin (see p. 268), begin with a greatly increased secretion of saliva, sweat, and tears; then nausea, profuse vomiting, and painful diarrhea; pupillary contraction and spasm of accommodation; pulse variable in rate, tense, and arhythmic; palpitation; dyspnea with râles; sometimes confusion of ideas, vertigo, tremors, and feeble convulsions. Death is either by paralysis of the heart or edema of the lungs.

Treatment.—Atropin is a physiologic antidote. Otherwise the general treatment of alkaloidal poisoning. For materia medica and therăpeutic uses, see end of chapter.

(F) CURARE GROUP.

I. MEMBERS, DERIVATION, AND CONSTITUENTS.

There are many drugs which have an action on muscle-nerve endings similar to that of curare, but with the greater number this action is overshadowed by other effects. The curare action is indeed so widely distributed that it may be looked upon as a peculiar expression of fatigue and as a sign of injury to these endings.

Among the most important poisons possessing this action are the following:

- Certain ammonia bases, amids and amins, cholin, muscarin, etc.
- Methyl-strychnin.
- Aromatic series: Pyridin, quinolin, thallin.
- Nicotin series, piperidin.
- Cocain.
- Camphor in frogs, but not in warm-blooded animals.
- Certain putrefactive ptomains.
- Products of muscle metabolism.

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[1] The edema produced by the drugs of this series consists rather in the aspiration of bronchial effusion, than in a true serous effusion. Injury to the walls of the capillaries is a necessary factor for the latter.

Curare is derived from the root-bark of South American plants of the genus Strychnos. It is prepared by the Indians as an arrow poison. The different samples which find their way into commerce probably have quite a different constitution. They are called Tiennas, Woorara, and Curare. Certain of them are also said to contain snake venom, but this appears to be erroneous. All these samples lose a great deal of their activity in time, and commercial curare is one of the most unreliable of drugs.

The constituents vary with the origin and also with the length of time during which the drug has been kept. They are alkaloidal in nature. The most important are:

Curarin,
Protocurarin,
Tubocurarin.

They decrease in activity in the above order, the curarin being the strongest.

II. SUMMARY OF ACTIONS.

1. Paralysis of the nerve endings in striped muscles.
2. Later, paralysis of the nerve endings around sympathetic ganglia.
3. With very large doses a direct depression of the irritability of the muscle substance.
4. Under special conditions a strychnin-like action on the central nervous system.

III. DETAILS OF ACTIONS.

1. Paralysis of Muscle-nerve Endings.—Ordinarily the only symptoms of "curare" poisoning consist in this paralysis. When the curare is introduced under the skin, it causes a total loss of motion, first of the voluntary and then of the respiratory muscles. The order in which this disturbance appears is the following:

(*a*) Short muscles of the toes, ears, and eyes.
(*b*) Limbs, head, and neck.
(*c*) Respiration.

The heart is not affected except with very much larger doses.

The first sign of curare action consists in incapacity for sustained effort on repeated stimulation of the nerve; *i. e.*, whereas a single contraction is normal, fatigue sets in more readily than usual. Then the height of contraction is somewhat lowered. Then the current must be strengthened to obtain any response; and finally even the strongest stimulation—of the nerve—is ineffectual.

It is evident that some structure is paralyzed. The paralysis might have its seat in any part of the central nervous system or it might be peripheral. Stimulation of the sciatic does not produce a contraction if the dose has been sufficient. The point of attack must, therefore, be peripheral to the sciatic nerve. This leaves the nerve-trunk itself, the nerve endings, and the muscle-fibers. Stimulation of the muscle directly is effective, so that this is excluded. To decide between the nerve-trunk and nerve endings, Bernard in his classical experiment placed a ligature around the body of a frog, with the exception of the sciatic nerves, and tightened the ligature so as to entirely exclude the lower extremities from the circulation. He then injected the curare. In this manner the peripheral portions of the sciatic nerves and the endings did not come into contact with the curare and the nerve-trunk was alone exposed to the poison. He found that stimulation of the trunk caused normal contraction, consequently that curare had no action on it, thus leaving only the endings.

The experiment can be performed in a much simpler manner by ligaturing one leg exclusive of the nerve, or by placing the muscle of one and the nerve of another muscle-nerve preparation into the solution.

This paralysis does not affect the *sensory nerves.*

The reports of early travelers who describe poisoning by curare-arrows mention that sensation is not impaired when motion is entirely impossible. Bernard also studied this action directly on the frog. He ligatured one leg with the exception of the sciatic nerve, injected the poison, and applied the stimulus to one of the upper extremities. This caused a reflex movement of the ligatured leg, which would not have been the case had the sensory endings of the foreleg been paralyzed.

In cold-blooded animals in which the respiratory exchange takes place largely through the skin, and respiratory movements are unnecessary, the poison is gradually eliminated if the animal be kept in moist atmosphere. Complete recovery occurs after eight to ten days, except when the dose is extremely large, in which case other factors come into play.

Warm-blooded animals die of paralysis of the respiratory muscles. If artificial respiration be kept up and the dose has been only just large enough to produce a paralysis, they may also recover.

The seat of the *respiratory paralysis* is also peripheral, for stimulation of the phrenic nerve does not cause contraction of the diaphragm.

2. Larger doses paralyze the nerve endings around the **sympathetic ganglia,** such as the vagus, vasomotor, salivary, pupillary, etc.

Stimulation of the vagus then usually only slows, but does not stop the heart. (Fig. 52 $\underset{\mathrm{I}}{\downarrow}$.) At this stage the pupil is little affected; later it is dilated (paralysis of oculomotor?). The heart is quickened, after a slight primary slowing (nicotin-like stimulation?).

3. The **circulation** remains almost normal long after the respiration has ceased; *i. e.*, if oxygen is freely supplied. The effects upon the heart and upon the blood-pressure

are very small, which makes curare an extremely useful drug in experiments in which the circulation must be kept normal. The objection to its use is that it does not cause sensory paralysis.

The *blood-pressure* falls, due to depression of the vasomotor ganglia. It does not come to complete paralysis, for the fall is abolished by strychnin, and reflex stimulation of the central end of the sciatic still causes a rise of pressure when stimulation of the peripheral ends is absolutely ineffectual on the muscles. (Fig. 52 $\downarrow_2$.) Later the curare may cause a slight rise, from quickening of the heart.

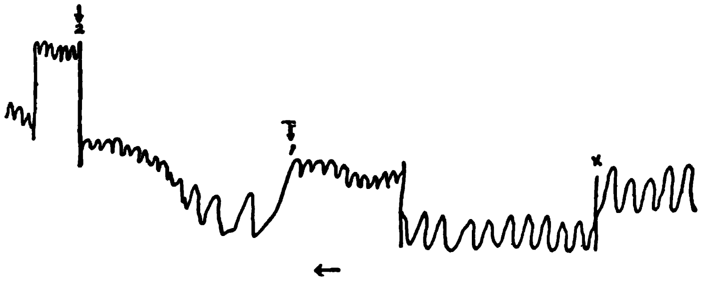

Fig. 52.—Curare. Carotid pressure, dog. The action begins at ×. There is first a fall of blood pressure, due to vasoconstrictor depression; secondarily a rise and quickening, due to vagus depression. Stimulation of vagus $\downarrow_1$ is effectual, but weak. Stimulation of sciatic $\downarrow_2$ causes rise of pressure although muscles are completely paralyzed.

An increase of *peristalsis* is often observed, but is probably due to asphyxia; so also are any changes in metabolism and largely the glycosuria.

4. Central Nervous System.—When curare is applied directly to the spinal cord it causes typical *strychnin convulsions.* With ordinary methods of administration these are, of course, masked by paralysis of the nerve endings, and besides it is very probable that the amount is not sufficient. Certain samples, however, cause strychnin convulsions before the typical curare action appears.

IV. RELATION TO OTHER GROUPS.

The chemic relation between curare and strychnin has already been mentioned, and it may be remembered that they are both derived from plants of the same genus. The *nicotin* series and curare are also related on account of their action on the sympathetic ganglia.

V. REASONS FOR INACTIVITY OF CURARE WHEN GIVEN BY STOMACH.

The effects of curare are obtained only if it is introduced under the skin or into the circulation, *not if introduced into the stomach.* The experiments on the administration of curare by the stomach have shown that—

1. It is not destroyed by the gastric juice.
2. It passes very slowly through the walls of the stomach when the epithelium has been killed, and not at all if the epithelium is still living. (It will be remembered also that strychnin is not absorbed by the stomach in rabbits.)
3. It is to a large extent fixed or destroyed by the liver, for it is much less active when injected into the portal than into the jugular vein. It is also distroyed *in vitro* by ox bile, and by bacteria.
4. It is very rapidly excreted unchanged in the urine.

The smallness of its action is, therefore, due to the capacity for absorption being less than the capacity for its destruction or excretion. If the renal vessels are tied, poisoning occurs quite readily even when it is taken by the stomach. If very large doses are taken on an empty stomach, sufficient may be absorbed to cause symptoms.

VI. TOXICOLOGY.

The toxicology of curare itself is at the present time of very little importance. The symptoms have been sufficiently discussed and consist of paralysis. In some cases in which it seems to have paralyzed the respiratory center before the muscles, it has given rise to asphyxial convulsions (or perhaps these were due to strychnin action).

Certain ptomains also exhibit a similar action.

The physiologic *treatment* would be the maintenance of artificial respiration until the poison has been excreted. The Indians use salt on the wound. This may be useful on account of the reflex stimulation which this causes when applied to an open surface.

VII. THERAPEUTICS.

Curare is a *laboratory drug.* It is of high importance in technic to immobilize an animal without producing any change in the circulation. It is also very useful when it is desired to investigate the properties of muscle exclusive of its nerve endings, etc.

Its *therapeutic application* is still largely experimental and not very promising. It has been suggested to combat the convulsions of strychnin, tetanus, and hydrophobia. It is certainly quite possible to suppress the spasmodic condition by sufficiently large doses. Unfortunately, however, it is impossible to secure this without at the same time paralyzing respiration. This latter may, theoretically, be counteracted by artificial respiration, but this prolonged manipulation is in itself injurious. On the other hand, minimal doses may be considered useless, and, indeed, as has been pointed out, even if the spasms could be suppressed without affecting the respiration, this would not be an ideal treatment for strychnin. In well-chosen cases, however, curare may be the means of saving life. Convulsions certainly tend to heighten fatigue and paralysis of the medullary centers, and if in a case in which the degree of poisoning just exceeded the lethal limit by a very little, a minimal amount of curare were injected, this might, perhaps, reduce the spasm sufficiently to turn the scale, or somewhat larger doses might be given which would require some, but not very much, artificial respiration. This has actually been done, and in desperate cases curare is worthy of a trial; but in addition to the other objections come the very uncertain quantitative effects. It would only be justified to work with tested samples, and these are very rarely accessible when needed.

(G) NICOTIN GROUP.

I. MEMBERS, CHEMISTRY, ETC.

Nicotin is a fluid, volatile, oxygen-free alkaloid, of strongly basic characters. It forms salts, most of which are soluble. It is colorless and almost odorless when freshly prepared; but it partly decomposes on keeping, acquiring a characteristic odor and a brown color.

The second member of the group, *piturin*, is a very similar, if not identical, alkaloid, derived from *Duboisia Hopwoodii*, which is chewed by the natives of Australia as tobacco.

The chemic structure of nicotin has been explained on page 153.

Although nicotin forms the only important ingredient of tobacco or its smoke, its action, when used habitually, presents sufficient difference to entirely separate it from the acute action.

(A) Acute Action of Nicotin (and Piturin).

This bears the greatest resemblance to that of pilocarpin, with the following exceptions:

The effects upon the central nervous system are more marked and are mainly depressing.

In glands and unstriped muscle, it paralyzes the ganglia exclusively; its action upon the eye shows some differences.

It has a curare action on muscle endings.

II. SUMMARY OF ACTIONS.

1. Depression of the central nervous system, preceded by short stimulation.

2. A stimulation, and more lasting paralysis, of sympathetic ganglia in all situations.

3. A curare action upon skeletal muscle endings, also preceded by stimulation.

III. DETAILS OF ACTION.

1. **Central Nervous System.**—Stimulation, followed by depression, of the whole cerebrospinal axis, from above downward.

The stimulation may be entirely absent, especially in large doses, so that the animal may drop dead almost instantaneously, without any other symptom. But this is not common.

The effects of small doses, such as are noticed in the first attempt at smoking, will be discussed later.

(A) Larger doses produce, from affection of the **hemispheres**, *excitement*, with violent headache. The former is transitory and soon gives place to *depression.*

In *frogs*, the symptoms are precisely the same whether the hemispheres are intact or removed, so that they do not play an important rôle in these animals.

(B) Of the **medullary centers** affected, the *respiratory, vagus, vasoconstrictor, and convulsion-centers* are the most important. It is possible that the salivation and vomiting are also partly of medullary origin. The stimulation of *respiration* finds expression in a quickening and deepening of the movements; in the subsequent depression, they are slowed, shallow, and irregular, and they are altogether arrested during the convulsions. Paralysis of respiration forms the *cause of death.* The circulation is more strongly influenced by the peripheral actions. The spinal cord also shows increased excitability, tremors, and heightening of reflexes, passing into *spasms.* These have their seat to a great part also in the hind-brain and medulla. They are very much weaker in anesthetized animals. Paralysis follows quickly on the stimulation.

2. **Peripheral Actions.**—These bear the greatest general resemblance to those produced by pilocarpin (see p. 271); so that the evidence brought forward for the latter applies with equal force to nicotin, with the exceptions about to be noted: The stimulation is shorter, and in large doses entirely absent, the depression more marked; the latter also becomes evident in the case of glands.

The effects of other drugs are the same upon the actions of nicotin as upon those of pilocarpin, except that comparatively much larger doses of nicotin than of pilocarpin are required to stimulate after atropin.

Where it is possible to investigate the nerve endings beyond the ganglia (as in frog's heart), it is seen that the endings are not affected by nicotin, except in the largest doses, and that the stimulation and paralysis reside in the *ganglia only*.

(*a*) On the *mammalian heart* the first effect is a *slowing* (Fig. 53, *a*), due to stimulation of the vagus ganglia, and also to that of the vagus center (see above). This is followed by marked *quickening and irregularity* (Fig. 53, *b*), from paralysis of the nervous mechanism.

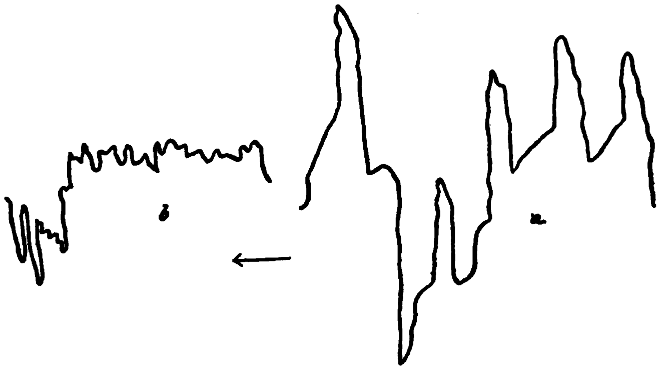

Fig. 53.—Nicotin. Cardiomyogram, dog. Upstroke = systole: *a*, First stage; *b*, second stage.

In addition, nicotin causes an increase in the irritability of the myocardium, so that it beats long after death; and even very large doses (as much as 12 Gm. in a dog!) have been stated not to be deleterious to the cardiac muscle; but the opposite view is held by most authors, and the whole series needs investigation in this respect.

(*b*) Of further effects upon the *circulation* (Fig. 54) there occurs a *rise in blood pressure*, due partly to the tachycardia, but mainly to vasoconstriction, particularly of the splanchnic vessels, which can be noted as a paling by direct observation. It precedes the quickening. The outflow from veins is lessened. It is again partly of central origin, but principally peripheral, since the rise occurs also after section of the cord. Its cause lies in a stimulation of the *constrictor ganglia*. Here also a paralysis follows; the vessels again become flushed and the pressure falls. But the rise of pressure may be evoked a number of times by repeating the injection, until finally the paralysis of the ganglia is complete.

(*c*) For ***unstriped muscle*** in general—***stomach, intestine, bladder, uterus***, etc.—the general remarks at the beginning of the section are almost sufficient.

There are ***nausea, vomiting, diarrhea***, and ***colic*** from its action on the ***alimentary canal***, even in small doses (smoking), doubtless for the most part from direct stimulation of the nervous mechanism, which is not so readily followed by paralysis in these muscles as in other organs.

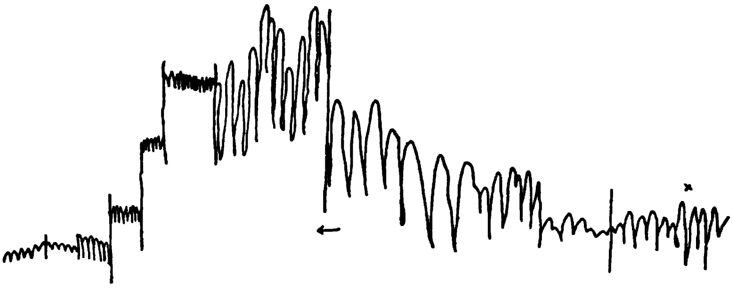

Fig. 54.—Nicotin. Carotid pressure, dog. The effect begins at ×. The beats first become weaker; then very slow and strong (vagus stimulation), with progressive rise of blood pressure (vasoconstrictor stimulation). Suddenly they become very rapid and consequently smaller. The total work of the heart is unchanged and consequently the pressure remains high; but the vasoconstrictors becoming paralyzed, the pressure soon falls. Later the heart-muscle also becomes weakened, as shown by the small beats.

A stimulation of the higher centers, both direct and as a reflex from the irritant action on the mucous membranes, may also play a part. But the importance of the peripheral action is shown by the fact that not only peristalsis, but even a tetanic spasm, may be induced by it in the *excised* gut, and at once abolished by atropin.

The *pupil* shows both contraction and dilatation at different times, nicotin acting upon the ganglia of both the oculomotor and sympathetic fibers. There may even be a direct action upon the iris muscle. The effect is different in different animals: The dog and cat usually show dilatation; the rabbit first constriction and then dilatation.

The general remarks already made suffice to define its action upon the *glands*.

(*d*) There remains only its action upon the endings of ***skeletal muscles***. These show at first ***fibrillary twitchings***, which disappear after the section of the nerves, but are started again by short stimulation of the nerve or muscle. They are abolished by curare, and must hence have their seat in the endings as well as in the central nervous system.

These twitchings are followed by typical curare paralysis (see p. 275).

In the milder stages this is shown by an equally strong, or stronger, current being required to obtain contraction when the stimulus is applied to the nerve than when it is placed on the muscle. In the normal preparation the opposite is the case.

Nicotin shows a further agreement with curare in its effects upon the ganglia (see p. 276). Curare, of course, acts more upon muscle, nicotin upon ganglia. Applied directly, it also paralyzes the nerve-fibers.

In *lower animals* the degree of toxicity of nicotin is determined mainly by the development of their central nervous system.

IV. TOXICOLOGY.

1. **Toxicity.**—Nicotin is one of the most fatal and rapid of poisons; the vapor arising from a glass rod moistened with it and brought near the beak of a small bird causes it to drop dead at once, and two drops placed on the gums of a dog may cause a similar result. The fatal dose for a man is about 60 mg.; of tobacco, about 2 Gm. It acts with a swiftness only equaled by hydrocyanic acid. And in view of the high nicotin-content of tobacco (one cigar contains a quantity of nicotin which would prove fatal to two persons, if directly injected into the circulation), also because of its popular distribution, it appears astonishing that fatal nicotin-poisoning is not more common; but just this wide distribution and knowledge of the drug form the safeguard, as also the marked taste.

Most cases of poisoning—outside of the slight ones from first attempts at smoking—have been produced by its medical application, especially by the laity; and since this has been largely abandoned, serious acute nicotin-poisoning has become very rare. It must be mentioned here that the application of tobacco to wounds or bruises is not at all without danger: since nicotin is volatile, it is absorbed from all surfaces, even from the intact skin, and fatal cases from this cause are recorded.

2. **Symptoms.**—In lighter cases, such as commonly occur in *smoking*, the peripheral actions predominate. There is first an increased flow of saliva, partly reflexly through the mechanical irritation of smoke, but mainly by direct stimulation of the ganglia through the nicotin. Nausea, vomiting, and diarrhea soon appear. The sweat-glands are also affected in a peculiar manner: There is a sensation of oncoming sweat, which does not actually break out. A sensation of exhaustion appears very early—partly as the result of nausea, but mainly as the first indication of central collapse action. Palpitation is also noted. Then come muscular incoordination, convulsions, and collapse.

The effects of poisoning with pure nicotin, which have been very carefully studied experimentally on *man*, bear the greatest resemblance to the above. After 1 to 4 mg. there were burning in the mouth, a scratching sensation in the pharynx, increased salivation, a sensation of heat spreading from the region of the stomach over the whole body; excitement with headache now appeared, then vertigo, confusion, disturbed vision and hearing, photophobia, dryness in mouth, cold extremities, nausea, vomiting, and diarrhea. Respiration quickened, but difficult. Pulse at first increased, then irregular. After forty-five minutes there was syncope, with clonic spasms. Recovery occurred, but a general depression persisted for three days.

3. The **treatment,** aside from the chemic, consists of coffee and other stimulants and in meeting the symptoms. Emetics will usually not be necessary.

4. The **postmortem appearances** are not characteristic, although large doses cause, in animals, anemia of the meninges and peculiar anatomic changes in the cortical nerve-cells. When taken by the mouth, there may be gastric and intestinal hyperemia, since nicotin is sufficiently alkaline to be somewhat caustic. The odor may furnish a valuable indication.

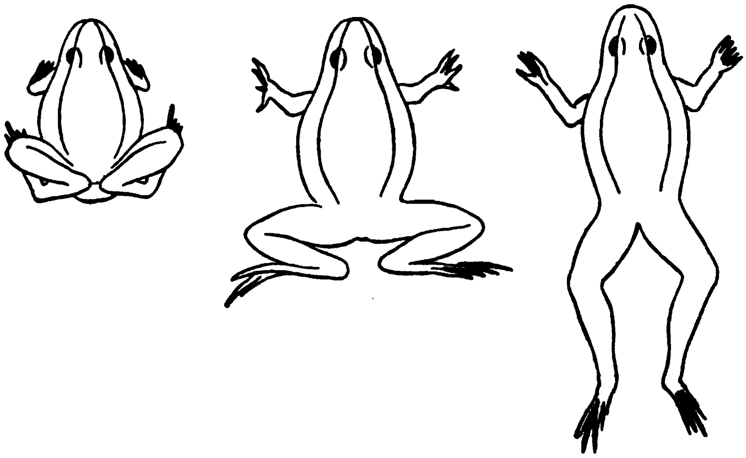

Fig. 55.—Nicotin. Successive positions of frog poisoned with 25 mg. nicotin.

The *proof* of the poison after its separation (see Chap. XXXIII) may be had by its odor and by obtaining its physiologic actions on frogs. The muscular tremors and the position which a frog assumes after nicotin are highly characteristic (Fig. 55). A control animal should, of course, be used.

The chemic tests are of no practical importance, since very similar reactions are given by coniin and by a ptomain.

The *excretion* of nicotin occurs mainly through the kidney, but also through the lungs and sweat. The neutralizing effect of the liver (see p. 136) is very marked in the case of nicotin.

Nicotin is very *resistant to putrefaction*, and has been isolated from the decomposed bodies of animals three months after death.

(B) Habitual Nicotinism.—I. Chemistry of Tobacco-smoke.—The effects of tobacco-smoke are due almost purely to the nicotin contained in it. The erroneous statement has been widely disseminated that this contained no nicotin. This view was based mainly upon theoretic deduction from the fact that the nicotin is present in tobacco in the form of a comparatively fixed salt. It was believed that the alkaloids in this form were burned by the heat of smoking. More exact recent researches have shown that under the conditions existing in smoking, the heat rises sufficiently high to set the nicotin free from its salt, yet not high enough to destroy it completely.

The effects of smoke upon frogs are precisely those of the nicotin contained in it. The drier the tobacco and the greater the heat, the less nicotin will escape destruction. In experiments something like 15 to 62% of the nicotin present in the tobacco are recovered from the smoke; but a greater part of this is exhaled or expectorated; this explains why a cigar, containing, as has been said, nicotin sufficient to kill two men, were it directly injected, has so comparatively small an effect. But even smoking may have a fatal result if a sufficient quantity of tobacco be consumed. There are no data concerning the percentage of nicotin in chewing tobacco.

The smoke, however, does contain *substances other than nicotin:* Aromatic essential oils; the decomposition products of nicotin: pyridin and quinolin; and the constituents of ordinary smoke: CO_2, CO, and HCN. All these are either almost without action, or the quantity is too small to have any serious effect. But if a large number of persons smoke in a confined atmosphere, the carbonic oxid may rise to a sufficient amount in quite a short time to produce a dangerous intoxication (see Chap. XX, A).

Smoked with an aspirator, the smoke from a

	CO_2.	HCN.	CO.	O.
Pipe contains, on average, . .	14.8	0.3	0.8	6.7%
Cigar, ...	13	0.4	3.3	10.5%

But this probably varies greatly with the manner of smoking. Arsenic is sometimes present in harmful quantities when Paris-green has been used on the plant as an insecticide.

All these smoke constituents, as also the volatile empyreumatic oils, concur with the nicotin to produce certain *local effects:* the biting sensation on the tongue, noted especially when the smoke is concentrated on one point, as in pipe-smoking. This constant local irritation also seems to favor the development of epithelioma. There is also a more general irritation of the mucous membrane of the mouth, throat, and pharynx, leading to catarrh and hoarseness. But these results follow only when the quantity consumed is very large or the smoker specially disposed.

II. General Effects.—The question of the effects of smoking has been largely discussed with a rather unscientific extremeness, some contending that it is entirely harmless when moderately used; whereas, on the other hand, an enthusiastic French writer has gone so far as to attribute the defeat of his nation in the war of 1870 to the prevalence of cigarette smoking. Of the two views, the former would seem to come nearest the truth if the stress is laid upon the word "moderate."

Since, next to caffein, nicotin is the alkaloid most widely used, an impartial discussion of this question is important.

1. Habituation.—To begin with, it must be acknowledged that the chronic use of nicotin presents very great individual variations in its consequences: Whilst one person may become easily accustomed to its use, another may be entirely unable to overcome the trial-stage, and others must be careful not to exceed a very limited amount. This variability depends not only on differences in the susceptibility of the individual, but also upon the manner of using the drug—whether or not the smoke is deeply inhaled, the saliva expectorated, etc.

The habituation is usually very rapid, and nicotin loses, in moderate doses, all its usual acute effects (we have noted a similar acquired immunity to some of the effects of belladonna and muscarin, see pp. 259 and 269; and it may also be interesting to note that the goat is comparatively immune to tobacco, as it is to atropin).

The fact that a second application of nicotin to a ganglion, etc., does not produce the original stimulation, is due to paralysis, and not to habituation. No habitual immunity has been clearly made out in animals, perhaps because sufficient experiments have not been made.

When this immunity has once been acquired, the continued use of tobacco within a certain individual limit produces absolutely no unpleasant symptoms; but if the limit be at any time sufficiently exceeded, the symptoms of chronic poisoning, presently to be discussed, arise. After a long time, some twenty years, these symptoms may also, but rarely, occur in those who have always kept within bounds.

Once the immunity to the usual acute action of nicotin has been acquired, its use by smoking, chewing, or snuffing brings with it a certain pleasant sensation, which appears to be entirely wanting with the beginner. This is somewhat difficult to define. There appears to be a certain repose, which, whilst it neither directly aids nor hinders the psychic processes, leaves the mind free, and in general raises the user's enjoyment of other pleasures, or lessens his annoyance at the opposite. The experience of recent campaigns appears to show that the use of tobacco enables soldiers to endure greater hardship.

How much of these effects is due to nicotin, how much to other factors, we cannot say. It is certain that the nicotin strength of the tobacco is not the determining feature of this action—rather the aroma. Smoking in the dark does not give as much enjoyment; and simply holding an unlighted cigar in the mouth, the chewing of other objects, etc., give similar, though much weaker, sensations. The truth would seem to be that it depends upon a reflex stimulation, from the mucous membrane of the mouth, nose, etc., in which the nicotin plays a part; and with this may be associated a direct action of the nicotin upon the central nervous system, at once stimulating and depressing.

2. *Chronic Intoxication.*—The symptoms from this are quite variable, but may be briefly stated as: *Functional arhythmia of the heart, digestive disturbances, depression of various parts of the central nervous system, and neuralgias.*

The first symptom to be noticed, the first warning, is occasional *palpitation*, the pulse-rate being at first quickened by depression of the vagus ganglia; if the nicotin is continued, this becomes quite persistent, but stops upon withdrawal; in advanced cases it may be necessary to continue the abstinence as long as six months or more. In the more advanced cases, the pulse may also be slowed. *Arhythmia* is always present. In still graver cases, the quickening and arhythmia may be extreme and approach to delirium cordis. Sudden *syncope* also occurs. *Respiratory distress* naturally accompanies the marked cardiac phenomena. The effects upon the heart are *functional*, not organic. Angina pectoris is so rare in these subjects that it must be attributed to causes other than the nicotin. On the other hand, *arteriosclerosis* appears to be favored by it.

The symptoms next in order are probably those arising from the *alimentary canal*, and depending upon the continued irritant action of the nicotin. These are: Loss of appetite, then dyspepsia and chronic intestinal catarrh, shown by alternating constipation and diarrhea. (On a moderate smoker the nicotin seems rather to have a tendency to keep the bowels regular.) These conditions lead to emaciation and anemia. A direct action upon the blood may also have a part in this; the continued administration of nicotin to animals leading to diminution of red corpuscles, and increase of leucocytes. It is also claimed that it diminishes the oxygenating power of hemoglobin. The nitrogen excretion is rather more diminished than the assimilation, so that there may be a gain in body-nitrogen.

Paralyzing effects upon the *central nervous system* become apparent; these are rarely of a serious nature. The *psychic functions* show a slowness and want of energy. Anxiousness and insomnia are quite frequent. There is a general muscular debility, tremors, and want of control over movements. The reflexes are heightened. Vertigo and a tabetic condition may set in. There is then an increase of excitability in the sensory and pain areas, and consequently headache and neuralgias; but the latter are in part due to referred pain from the cardiac disturbances. They are often early and quite characteristic, and take the form of pain and *hyperesthesia* in the precordial region, left nipple, and ulnar surface of left arm.

The *special senses*, and especially *vision*, are also affected. The latter becomes dim and the accommodation faulty; miosis is frequent. These conditions are at first readily removed by withdrawal, but in advanced cases they may lead to an atrophy of the optic nerve.

Transitory aphasia is also an occasional phenomenon, and so is transitory albuminuria, the latter due to irritation of the kidneys by the excreted nicotin.

Of other effects which have been attributed to nicotin, but with insufficient cause, may be mentioned, impotence, epilepsy, and insanity.

3. Treatment.—It will be seen that the catalogue of injurious actions to be charged against the abuse of this drug is sufficiently large; but on the other hand, it must be noted that these are absent with moderate use, and can be abolished if the use of the drug is promptly limited on their first appearance. Actual withdrawal is not always necessary.

Limitation in quantity, the use of tobacco poor in nicotin, sufficient expectoration, and the avoidance of deep inhalation of the smoke, are often sufficient. Quick total withdrawal does not lead to abstinence symptoms, as with morphin (except possibly in some especially neurotic subjects), although it may disturb the function of the bowels for a few days. The principal point in the treatment is to keep the thought of the patient off the topic of tobacco, and to supply the accustomed stimulus to the mouth in some other manner, as by chewing ginger or gentian.

The use of tobacco must, of course, be avoided in pathologic conditions in which there are special contraindications to it—in heart disease, dyspepsia, inflammation of the respiratory tract, etc.

Tabacum (U. S. P.) (Tobacco).—"The commercial dried leaves of Nicotiana Tabacum, Linné, (N. O. Solanaceæ)." An annual plant, probably indigenous in tropical America, and now cultivated in most parts of the world. The annual production of the world is estimated at a million tons (1,000,000,000 kilograms). Other species also contain the nicotin. The plant was introduced into Europe shortly after the discovery of America. Its use by smoking was practised by the natives at the time of Columbus.

The important constituents are nicotin, which is also present to a less extent in all other parts of the plant, and a volatile oil developed in drying and "sweating." The percentage of nicotin varies between one and eight per cent.: In Havana and Maryland, 1.5 to 3; Virginia and Kentucky, 6 to 8; South America, 2 to 6; Germany, 1.5 to 3. Three other alkaloids have also been announced to exist in small amount in tobacco.

The cultivation of tobacco requires a great deal of care. The plants are first grown in seed beds, and later transplanted into fields. Only particular climatic and soil conditions will give good tobacco, and even the fertilizers must be carefully selected, since they will have an effect upon the ash. The variety of the tobacco depends largely upon the soil; a light sandy soil giving thin, light-colored wrapper leaves, and a heavy rich clay giving dark, thick fillers. But often wrappers and fillers are taken from the same plant. The plants are "topped" so as not to produce seed, and when the leaves are ripe—*i. e.*, when they begin to change color, become spotted and break easily—they are cut. These fresh leaves are practically odorless, the odor becoming developed in wilting, and especially by fermentation through enzymes. The substances which give rise to the ethereal oils are little known—they appear to be of the nature of glucosids. And these oils themselves are present in only very small quantities—100 kg. of Brazilian tobacco having yielded only about 20 Gm. Extreme dilution does not destroy their aroma. The quantity of these oils varies often, but not always, with the nicotin-content.

The development of aroma is not the only step necessary in the preparation; it is quite essential to destroy substances present in the leaves—mainly of proteid and fatty nature—which would give the smoke a very unpleasant odor. This is done by "curing." Curing is also a fermentation, having for its object the destruction of these proteid substances by bacterial action. It is accomplished essentially by piling the tobacco in a warm, moist place to secure the conditions favorable to the action of the bacteria. It is often aided by dipping the leaves into saccharine solutions (molasses, cider, etc.). These are often flavored ("pituring") with anise, cinnamon, etc. But few tobaccos, naturally poor in proteids, such as some Havana and Asiatic varieties, can be used without this curing, which is an undesirable feature, since some of the aroma and nicotin are also lost in the process—the more, the longer it is carried on. To restore this, the leaves are sometimes soaked in infusions of tobacco stems, etc.

The cured tobacco has only a slight odor; the real aroma is brought out in the "sweating"—a later fermentation, taking place also in stored tobacco. In this process one-fourth to one-third of the nicotin disappears.

No preparations of tobacco except the dried leaves are official; if used, an infusion may be made.

(H) MINOR MEMBERS OF THE SERIES.

1. CONIUM.

I. Composition.—Conium (Water-hemlock) contains a *number of alkaloids:*

Coniin, $C_8H_{17}N$ Methyl-coniin, $C_8H_{16}N.CH_3$
Conicein, $C_8H_{15}N$ Conhydrin $C_8H_{17}NO$.

They *differ only in the strength of their action.*

The commercial coniin consists of a mixture of the above, and as this alone has been employed on man, the following remarks apply to this mixture. As these alkaloids decompose very rapidly, the commercial preparations are often entirely inactive.

II. Summary of Actions.—Coniin bears a very *close resemblance to nicotin* in its physical and chemic characters, in its composition and actions. The latter differ in a more pronounced paralysis of the central nervous system and of the endings in striped muscle. For chemic structure see page 152.

(The mother-substance, piperidin, has a similar but weaker action.)

III. Details of Action.—1. Peripheral Organs.—It stands here midway between curare and nicotin (see p. 283), paralyzing both motor endings and ganglia, and forming with the other members a series running:

Action on motor endings predominates:

↑ Curare
Coniin
Gelseminin
Spartein
Nicotin. ↓

Action on ganglia predominates:

Its action on the pupil, heart, blood-vessels, circulation, alimentary canal, glands, etc., is precisely as in nicotin, only weaker.

The muscle substance is not affected. Applied directly to the skin it diminishes sensation.

2. In its action upon the **central nervous system**, the resemblance is also very great, but the stimulation is still less, and the *depression* is so strong that it forms the most prominent feature of poisoning in man. *Consciousness* is little or not at all affected, the main symptoms referring to the motor system, and these are very characteristic. The paralysis is *ascending*, beginning with the lower extremities, and finally reaching the *tongue*, so that the patient may be unable to speak whilst his intellect is not yet disturbed.

This ascending paralysis has been explained by a lowered *conductivity* of the cord to impulses coming from the brain, the path being blocked at first only to those impulses which have a long way to travel.

The *excitability* of the cord is not decreased, however, so that *convulsions* may appear. These can occur only in mammals, since the curare action is an early feature in the frog; and this undoubtedly plays its part also in the paralysis in man.

Depression of the medullary centers is also a prominent feature, and death occurs by *paralysis of respiration*. This is also due in part to the curare action.

IV. Toxicology.—Coniin is *much less toxic than nicotin;* 85 mg. do not produce as violent symptoms as 4 mg. of the latter; but this may be partly due to the fact that the pure alkaloid was not employed. The *symptoms* are very characteristic, and they have been so well described in Plato's classic rendering of the death of Socrates, that no difficulty is experienced in recognizing the substance used in the poisoning of this philosopher. The description is so accurate that it may well serve to represent the usual *symptoms*.

After drinking the poison, "He [Socrates] went about, and as he noticed that his thighs became heavy, he laid down on his back, as the man directed. The latter—the one who had given him the poison—touched him from time to time, and investigated his feet and thighs. Then he pressed his foot strongly, and asked whether he could feel it; he answered, No. Then he tried the knees, and so went higher and higher, and showed us how he gradually became cold and stiff. Then he touched him once more, and said, when it came to the heart, then he would be dead. Now almost everything from the abdomen down was cold," and Socrates then spoke his last words to his friends, but was unable to answer further questions. He had a short spasm and was dead.

From the quick action, it is supposed that he must have been given the expressed juice of the root, and it is very probable that the Greeks commonly used their poisons in this form.

Coniin may be *recognized* by its characteristic narcotic odor. Like nicotin, it is liquid, colorless, becoming brown in air. The test consists in the curare action on injection in the frog. The chemic reactions are of little value, since they resemble nicotin very closely, and are given by a ptomain.

2. LOBELIN.

Lobelin, the alkaloid of Lobelia inflata, has an action essentially the same as nicotin in so far as it has been studied.

Small doses stimulate, large doses paralyze, the respiratory center. The vagus endings in bronchial muscle are also depressed.

Anagyris fœtida, a leguminous plant indigenous to the shores of the Mediterranean, and there used as a substitute for senna, contains an alkaloid, anagyrin, whose pharmacologic actions resemble those of lobelin in many respects.

3. GELSEMININ.

Gelseminin, the active alkaloid of gelsemium, produces *effects in general almost identical with those of coniin* (see p. 290). Its *depressing action* on the central nervous system is more marked than that of the latter, so that the central paralysis precedes the peripheral even in frogs.

It has a very decided *mydriatic effect* upon the pupil, especially on local application. This is believed by some to be due to paralysis of the oculomotor endings after the manner of atropin ; but the question cannot be considered as definitely settled. The mydriasis lasts from twelve to seventeen hours.

(*Gelsemin*, another alkaloid, has an extremely weak strychnin action. The commercial "Gelsemin" is a mixture of both alkaloids, owing its activity to Gelseminin.)

4. SPARTEIN.

The last member of this series is spartein, a liquid, oxygen-free alkaloid existing with a neutral principle, scoparin, in the *broom plant.*

Spartein, while showing a close general resemblance to coniin, presents some important *differences :*

The *central actions are weaker*, the ***peripheral stronger.***

In the *heart* it appears to act on the muscle also, making it *slower and weaker* (it cannot, therefore, be classed with digitalis, as is sometimes done; for the latter, although it slows the heart, strengthens the contractions). The *blood pressure is usually lowered* when the drug is taken by the mouth, since the depression of the heart is more than the constriction of the vessels which it also produces.

The diuretic action of broom-top is not due to the spartein, but to the scoparin, and will be discussed later.

(I) PHYSOSTIGMIN (ESERIN).

This should probably be placed with muscarin, as stimulating precisely those structures which are paralyzed by atropin: the nerve endings in certain organs. But its antagonism to atropin is much more complete, and it starts the heart after muscarin; also, it acts on striped muscle; so that we are almost forced to accept in addition some direct stimulation of the muscle or gland cells themselves.

I. SUMMARY OF ACTIONS.

1. Stimulation of endings and cells of all muscles, striped, unstriped, and cardiac; and of certain glands.
2. Paralysis of the central nervous system.

II. DETAILS OF ACTIONS.

1. **Striped Muscle.**—In mammals these exhibit peculiar fibrillar contractions, persisting after the section of the nerve. They are diminished, but not abolished, by moderate doses of curare, showing that the stimulation resides only partly in the endings; and the view that the muscle-fiber is *stimulated in part directly* is also supported by the fact that its working power and irritability are increased.

2. The contraction of the **cardiac muscle** is slowed but strengthened (Fig. 56, *A*). This slowing occurs even after atropin, showing that its cause is at least largely independent of the vagus. The amplitude is first increased, then diminished. Strong doses cause systolic standstill of the frog's heart. The *blood pressure rises* at first; this rise depends only in small part upon the strengthened heart, since this is largely counteracted by the slowing. Nor is it due to stimulation of the vasomotor center, direct or reflexly through convulsions, since it occurs in curarized or chloralized animals. Its cause lies in the *direct peripheral stimu-*

lation of the arterial muscle, aided by the violent peristalsis. The rise of blood pressure is followed by a *fall* due to paralysis of the vasomotor center (Fig. 56, *B*). On account of its action on the cardiac muscle, physostigmin will start the frog's heart which has been stopped by muscarin; and this can now be stopped only by poisons which directly depress the cardiac muscle, such as copper salts or apomorphin.

3. By stimulation of the **unstriped muscle** it causes violent peristalsis,[1] vomiting, and contraction of bladder, spleen, uterus, arterioles, and bronchial muscles.

4. Upon the **eye** its action resembles that of muscarin, except that it antagonizes atropin much more completely. It causes contraction of the pupil and spasm of accommodation, and as a consequence of the miosis there occurs a marked fall of intraocular pressure. Since the radial muscle is stimulated as well as the sphincter, the contraction is not so complete as with muscarin. The action consists mainly in a stimulation of the oculomotor endings, for it does not act after all the nerve endings have been degenerated by section of the nerves. There also seems to be stimulation of the oculomotor center. Atropin widens the pupils somewhat after physostigmin-constriction.[2]

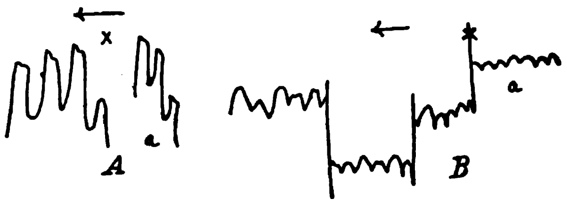

Fig. 56.—Physostigmin (after atropin, *a*). The action begins at ×. *A*, Cardiomyogram, dog. Upstroke is systole. Shows stimulation of muscle by strengthening and slowing. *B*, Carotid pressure, dog. Shows first vasomotor paralysis by fall of pressure, then slowing and strengthening by action on cardiac muscle. This again brings up the pressure.

5. The **glands**, especially the salivary, mucous, lachrymal, and sweat-glands, are stimulated by physostigmin; and since it acts promptly after atropin, its

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[1] Its direct application causes localized contraction rings, so that its action appears to be largely muscular.

[2] We have occasionally seen a dilatation of the pupil in frogs' eyes placed in physostigmin solution, but have not determined the cause of this abnormal action. It does not seem to lie in the solution, for the same solution contracted other pupils.

action here, as elsewhere, is probably partly on the gland-cells themselves. The increase of secretion is, however, not nearly so marked as with the other members of the series, since it is *counteracted by the constriction of the blood-vessels.*

6. On the **central nervous system,** its action is rapidly paralyzing, *beginning*, at least in man, in the *lower portions*, so that *consciousness is preserved* to the end. There is a primary stimulation,—excitement, etc.,—but this has been considered as *secondary to respiratory paralysis.* Dyspnea is a marked symptom, due to paralysis of the respiratory center and spasm of the bronchial muscles. Asphyxia forms the *cause of death.*

III. TOXICOLOGY.

The **symptoms** are readily explained by its actions. There are nausea, vomiting, and diarrhea; salivation, lachrymation, and sweating; palpitation with slowed pulse; miosis; excitement and dyspnea; weakness with muscular twitchings; convulsions. Death by paralysis of respiration under general collapse, the reflexes persisting to the end.

Treatment.—General alkaloidal. Physiologic antidote: atropin and strychnin.

Proof.—Its physiologic action upon the eye is among the most characteristic.

As physostigmin is very readily decomposed by light (solutions acquiring a reddish color and losing much of their activity), its search must be conducted, as far as possible, in the dark, and the employment of heat should also be minimized.

(K) RÉSUMÉ OF THE SERIES.

I. METHODS OF STUDYING.

1. **General Remarks.**—A *paralysis* is localized by stimulating above and below; the latter is effective, the former is not.

A *stimulation* is localized by paralyzing above and below; the latter stops it, the former does not.

It must be remembered that a slight degree of paralysis may be overcome by a strong stimulation; also, that a paralysis *above* a stimulation may appear to lessen the latter, if it has been previously supported by normal central tonic impulses.

2. Particulars.—Stimulation or paralysis may be done (1) *electrically* or by section.

- Heart, . . .
  - Cardiac vagus: trunk, postganglionic (sinus).
  - Cardiac accelerator: trunk.
  - Cardiac muscle.
- Eye, ...
  - Oculomotor (preganglionic).
  - Oculomotor and short ciliary (postganglionic).
  - Cervical sympathetic (preganglionic).
  - Cervical sympathetic and long ciliary (postganglionic).
  - Muscular fibers.
- Submaxillary:
  - Chorda tympani and cervical sympathetic (preganglionic).
  - Hilus (postganglionic).
  - Cells.

2. *Drugs* (in appropriate doses).

- Paralysis, . .
  - Cells: Apomorphin, copper.
  - Nerve endings: atropin.
  - Nerve-ganglia: coniin.
- Stimulation:
  - Cells: Physostigmin.
  - Nerve endings: Muscarin.
  - Nerve-ganglia: Nicotin.

It must be remembered that the action of the different members is not marked off absolutely sharply. They all stimulate and then paralyze, and they all affect every portion of the nerve-ganglion-ending-cell chain.

II. MAIN PERIPHERAL ACTIONS OF DIFFERENT MEMBERS OF SERIES.

Atropin: Paralysis of endings in glands and unstriped muscle. Strong solutions: Stimulation, then paralysis, of muscle-fibers.

Muscarin: Stimulation of endings in glands and unstriped muscle.

Physostigmin: Stimulation of endings and cells.

Pilocarpin: Long stimulation of ganglia and endings, followed by very late paralysis.

Nicotin, *Gelseminin*, *Lobelin*, *Spartein:* Long stimulation of ganglia, followed more quickly by paralysis.

Curarin, *Coniin:* Paralysis of ganglia (and muscle-nerve endings).

III. ACTION ON PARTICULAR ORGANS.

1. Heart: Vagus Mechanism.—**(a) Ganglia:** ***Nicotin***, ***pilocarpin***, ***lobelin***, ***gelseminin***, and ***spartein*** produce stimulation followed by paralysis. *Curarin*, *coniin*, and *cocain* produce almost pure paralysis.

(b) **Postganglionic Fibers (Endings of Vagus):** Stimulated by *muscarin* (*pilocarpin*, *physostigmin*), *thyroidin*, [sodium phosphate, digitalis, etc.]. Paralyzed by *atropin*, *sodium iodid.*

(c) **Muscle-fiber:** Stimulated, then paralyzed, by *atropin*; almost pure stimulation by *physostigmin* (veratrin, digitalis, camphor, etc.); almost pure paralysis by apomorphin or copper salt.

2. **Pupils.**—(a) **Stimulation of Dilator (Sympathetic) Endings and Ganglia:** *Cocain.*

(b) **Paralysis of Constrictor (Oculomotor) Endings:** *Atropin* (*gelseminin* ?).

(c) **Stimulation of Constrictor (Oculomotor) Endings:** *Physostigmin*, *muscarin.*

The other members of the series may act upon either mechanism.

3. **Glands.**—(a) **Ganglia:** Stimulated, then paralyzed, by pilocarpin and nicotin. In case of former, paralysis comes very late.

(b) **Endings:** Stimulated by muscarin, pilocarpin, physostigmin. Paralyzed by atropin.

IV. EFFECT OF MODERATE DOSES UPON:

1. **Blood pressure.**

Atropin: Rise, mainly through vagus paralysis.

Nicotin, Pilocarpin: Rise with slowing. Former mainly stimulation of vasomotor ganglia, latter of vagus. Later quickening with further rise, then fall.

Curare, Conium: Mainly fall through vasomotor paralysis—both central and peripheral.

Physostigmin: First rise, but mainly fall through paralysis of central nervous system.

2. **Heart-rate.**

Atropin, Curarin, Coniin: Quickens.

Pilocarpin, Nicotin: First slowed, then quickened.

Physostigmin: Slowed.

3. **Pupil.**

Dilated: Atropin, cocain, gelseminin, nicotin, coniin.

Constricted: Muscarin, physostigmin, pilocarpin.

4. **Peristalsis.**

Arrested by atropin, quickened by all the others.

TABLE XIII.—DRUGS ACTING PERIPHERALLY UPON GLANDS AND UNSTRIPED AND CARDIAC MUSCLES.

	CENTRAL NERVOUS SYSTEM.	GANGLIA.	PERIPHERAL ENDINGS IN GLANDS AND UNSTRIPED AND CARDIAC MUSCLES.	DIRECT ACTION ON CARDIAC AND UNSTRIPED MUSCLES.	ENDINGS IN SKELETAL MUSCLES.	SECRETIONS.	HEART.	PUPIL.	PERISTALIS.
Tropeins, . .	Stimulation, then depression.	None.	Paralyze.	Short stimulation and in large doses paralysis.	Slight curare.	Diminished.	Quickened.	Dilated.	Diminished.
Muscarin, . .	Stimulation, then depression.	None.	Stimulates.	Large doses paralyze.	Curare action.	Increased.	Slowed.	Constricted.	Increased.
Curare, . . .	Stimulation, then depression.	Short stimulation, then paralysis.	None.	None.	Paralyzes.	Diminished.	Quickened.	Constricted.	Diminished.
Lobelin, . . Pilocarpin, . Nicotin, . .	Mainly depressing.	Short stimulation, then paralysis.	Pilocarpin produces stimulation, others no effect.	Like atropin.	Stimulate, then paralyze.	Increased.	Slowed, then quickened.	Variable.	Increased.
Coniin, . . Gelseminin, Spartein, .	Mainly depressing.	Short stimulation, then paralysis.	None.	Like atropin.	Stimulate, then paralyze.	Increased.	Spartein permanently slowed.	Dilatation.	Increased.
Physostigmin,	Mainly depressing.	None.	Stimulates.	Stimulation.	Stimulate.	Increased.	Slowed.	Constricted.	Increased.
Apomorphin, .	Mainly stimulation.	None.	None.	Depression.	None.	(Increased through nausea.)	Slowed.	None.	Diminished.

(L) THERAPEUTICS OF PILOCARPIN SERIES.

Of the actions of this series, the peripheral effects of *pilocarpin* are almost the only ones which attain to a practical importance. Nicotin, as well as the other members, possesses few, if any, advantages over it, and on the other hand, a number of *other undesired* and more or less violent *actions*, especially the depression of the central nervous system, the irritant action on the alimentary canal, and the cardiac disturbances. These are much less marked in the case of pilocarpin, so that they may be entirely avoided in ordinary doses. But it has been attempted to use some of the *special actions* of the others:

1. **Coniin** has a depressant action on the central nervous system and a curare effect upon muscle. This would justify its employment in *spasmodic conditions*, such as strychnin-poisoning or any other tetanus, in chorea, whooping-cough, torticollis, etc. It would possess the advantage over curare that it acts on the seat of the disease—centrally—as well as peripherally. Its usefulness is much lessened by the uncertain strength and action of its preparations, due to their ready decomposition.

2. **Lobelia** has been used as an emetic, but it possesses no advantage over apomorphin or emetin, is more depressant, unreliable, and if vomiting does not occur, it produces very violent symptoms. The preparations also vary much in strength.

3. **Gelsemium** is used both locally and internally as a mydriatic, but is inferior to atropin.

4. **Spartein** has often been tried to raise the work of the *heart* and produce moderate slowing. It does the latter, but not the former, according to experimental and the bulk of clinical evidence; it is therefore of no value in heart disease, or, at most, only in the same cases as aconite. Doses of 0.01 Gm. ($\frac{1}{6}$ grain) are specific in some cases of asthma. The broom plant contains another principle, scoparin, which makes it of value as a diuretic in fevers, etc. This will be considered later.

5. **Physostigmin** has been tried as a *nervous depressant* in epilepsy, chorea, tetanus, etc. The results have not been satisfactory, perhaps because a sufficient dose cannot be given without bringing on respiratory disorder.

Its peripheral actions—sweat, *peristalsis*, etc.—also cannot be obtained sufficiently pure on systemic administration, so that pilocarpin is preferred to it. It has been given in atony of the intestine, but is dangerous.

Its usefulness is therefore limited to **ophthalmologic practice.**

The *lowering of intraocular pressure* makes it *the* remedy in *glaucoma;* and the miosis is used in alternation with atropin to break up *adhesions of the iris to the lens*—a condition now generally treated by operation, however. It may be used to counteract the *paralysis of accommodation following atropin.*

It is used for its effects on the eye locally in *1% solution* (of the salicylate). The miosis begins in five to fifteen minutes, reaches its maximum in half an hour, and passes off for the most part in an hour, but little effect remaining after this time. The effect upon accommodation begins somewhat later and is more lasting.

6. With **pilocarpin** the *stimulation of the salivary and sweat glands* is the most prominent and among the earliest actions, so that it may be obtained almost free from any of the other effects. The alkaloid is to be preferred. The preparations of the crude drug lie longer in the alimentary canal and have therefore more opportunity to exert the objectionable action here. And, further, the jaborin may very largely neutralize the pilocarpin in many samples.

The increased secretion leads first to a *removal of liquid* from the body, and with this, of *waste and toxic products* of all kinds. The former indicates it in all conditions where there is an *accumulation of fluid,* especially when of renal origin; in dropsy, effusion into retina or brain, etc. It not only removes the accumulated fluid, but also *relieves the kidneys* of a part of their work. The removal of fluid pressing upon the veins, etc., leads to an *improvement in the general circulation,* and thus removes also the congestion of the kidneys; in consequence—and not by any direct action—the *quantity of urine* is increased. Its main indication in dropsy, then, is in that of renal origin, not nearly so much when the disease is cardiac; for here its tendency to depression of the heart and circulation in general vitiates its beneficial effects.

The removal of toxic products from the body makes it useful in *uremia,* in *chronic opium-poisoning,* etc.

So much for its effects upon secretion as a whole.

The increases in sweat, saliva, mucus (and milk), are in particular utilized practically. For its use as a sudorific see below. The increased action of the *sweat glands* brings with it an increased **circulation in the skin,** and this secondarily increases the *growth of the hair,* and, it is claimed, also turns it to a darker color. It may be used for the former purpose. Its **sialogogue action** [1] is employed against poisons which suppress this secretion, as those of the atropin group and certain meat-poisons. The increased secretion of *mucus* makes it useful in all cases of *dry cough* (see Chap. XXIII, C), and this action is aided by its nauseant properties. It may also result in loosening false membrane in *croupous conditions*, and be the means of saving life. This liquefying action on the mucus, as well as their action on the respiratory center, has determined the use of pilocarpin, tobacco, and lobelia in *asthma* (see p. 262). Similarly the increase of biliary mucus facilitates the passage of *gall-stones.*

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[1] Sialogogues (measures which increase flow of saliva) may be divided, according to their action, into:

(*a*) Those which stimulate the nervous mechanism of the salivary glands directly: Pilocarpin, physostigmin, etc.

(*b*) Those which stimulate the nervous mechanism of the salivary glands reflexly: Acids, sapid substances, alcohol, local irritants (saponins), nauseants.

(*c*) Those which irritate the gland cells: Mercury, iodids, ipecac, etc.

An increase in the secretion of milk may perhaps be considered doubtful.

Its *nauseant action*, and that on *peristalsis*, could possibly be utilized therapeutically; but it is inferior in these respects to other remedies (see Chaps. XIV, C; and XXXII), and these form rather *unpleasant side-actions*, partly directly and partly by the general depression which they produce.

The *slowing of the heart* produced by the members of this series is of no practical importance, since it cannot be obtained sufficiently pure. The constriction of the *pupil* and lessening of intraocular tension have caused pilocarpin to be used as a *substitute for physostigmin* in glaucoma (see p. 300). It has no advantage over the latter drug, its action being shorter and less complete. A 2% solution is employed locally.

The action on the *uterus* may result in abortion, but cannot be used in practice, since the doses required for its action on this organ are dangerous.

Lastly, it forms the physiologic *antidote to atropin* and certain snake-venoms (rattlesnake).

(M) DIAPHORETICS.

Diaphoretics (sudorifics or hydrotics) are remedies which increase the secretion of sweat, an object which may be attained in the following manner:

(*A*) *By affecting the circulation in the skin:*

Locally: 1. Local irritation.

Systemically: Indirectly: 2. Rise of general blood pressure if cutaneous vessels are not simultaneously constricted.

1. **Removal of Liquid from the Body:**

(*a*) to cause the *absorption of exudates*.

(*b*) in *obesity*, withholding carbohydrates at the same time, to oblige the body to form the water which it requires, by the combustion of its adipose tissue.

For these purposes any of the diaphoretic measures, with the exception of hot liquids, may be used, either singly or in combination.

2. **Removal of poisons** introduced from without or formed in the body: this is especially valuable in chronic intoxications, as by As, Pb, Hg; nicotin, morphin, bacterial poisons (in fevers, etc.); snake and spider bite; uremia, gout, myxedema, etc.

3. **To re-establish disturbed circulation** in the skin, and thereby to *relieve congestion* of internal organs: this determines their use in colds, rheumatism, etc.; in cold skin from whatever cause; in inflammation of lungs, pleura, etc. When a strictly local congestion is to be relieved, the same results may be obtained by counterirritants (see Chap. XXIX).

The increased vascularity of the skin is also used to hasten the outbreak of *febrile exanthemata*, *to promote the absorption of salves, etc.* Further, in certain *diseases of the skin* where its nutrition is defective.

4. **To Relieve Inflamed and Overtaxed Kidneys.**—The amount of excrementitious material removed by a thorough sweating is really quite large, and this gives the kidneys a good measure of functional rest.

5. **To increase the alkalinity of the tissues,** in gout, oxybutyric acid coma (diabetes), etc. Drugs which stimulate the glandular activity directly, such as *pilocarpin*, must be employed here, since the sweat is acid only when produced in this manner. This removal of acid is so marked that the urine of healthy individuals may be made markedly alkaline by an injection of pilocarpin.

(N) MATERIA MEDICA.

(* *Muscarin*, not used; dose would be 10 to 100 mg.)

Pilocarpus (U.S.P.) [**Jaborandi Folia**, B.P.].—*Jaborandi*.—Leaflets of *Pilocarpus Selloanus* and *P. Jaborandi*, Rutaceæ. Brazil.

Pilocarpin (¼ to ½ %), Pilocarpidin, Jaborin, and Jaboridin (last two have atropin action); Gums; Volatile Oil.

* Not official.

Extractum Pilocarpi Fluidum (U.S.P.) [Extr. Jaborandi Liquidum, B.P.].—One-half alcohol (U.S.P.) [Alcohol, B.P.]. Turbid with water. *Dose:* 0.3 to 2 c.c. (5 to 30 minims).

Tinctura Jaborandi (B.P.).—20%. One-half alcohol. *Dose:* 2 to 4 c.c. (30 to 60 minims).

⁂ *Pilocarpinæ Hydrochloras* (U.S.P.).—Very soluble. *Dose:* 0.005 to 0.02 Gm. (⅛ to ⅓ grain), usually hypodermically. Local use on eye: 2%.

⁂ *Pilocarpinæ Nitras* (B.P.).—Soluble in 9 parts water. *Dose* as above.

* **Curara.**—The important constituents have already been noted. The different samples of the drug vary so widely that no dose can be set down. Of an average active sample 0.008 to 0.04 Gm.—of curarin, 0.0025 to 0.03 Gm.—intravenously, have been stated to be efficient in man.

Tabacum.—The dried commercial leaves of *Nicotiana Tabacum*, Solanaceæ; cultivated. Obsolete. The dose is given as 0.5 Gm.

* *Nicotin.* ** The dose would be to 0.001 Gm.

Conium (U.S.P.) [**Conii Fructus**, B.P.].—(*Spotted Hemlock.*) Fruit of *Conium Maculatum*, Umbelliferæ. Europe and Asia; naturalized in North America.

Conii Folia, B.P.

The principal constituents have been given.

The *preparations* are not reliable:

Extractum Conii (U.S.P.).—One-half alcohol, with addition of acetic acid. *Dose:* 0.015 to 0.06 Gm. (¼ to 1 grain).

Extractum Conii Fluidum (U.S.P.).—Same menstruum. *Dose:* 0.06 to 0.3 c.c. (1 to 5 minims).

Succus Conii (B.P.).—3% of the juice. *Dose:* 4 to 8 c.c. (1 to 2 drachms).

Unguentum Conii (B.P.).—From the juice.

Tinctura Conii (B.P.).—20% in three-fourths alcohol. *Dose:* 2 to 4 c.c. (30 to 60 minims).

* *Coniin.* ** *Dose:* 0.002 to 0.005 Gm.

Gelsemium (U.S.P.) [**Gelsemii Radix**, B.P.].—(*Yellow Jasmine.*) Rhizome and roots of *Gelsemium sempervirens*, Loganiaceæ. Southern United States.

* Gelsemin and Gelseminin; Volatile Oil; Resin.

Extractum Gelsemii Fluidum (U.S.P.).—Alcohol. *Dose:* 0.3 to 0.6 c.c. (5 to 10 minims).

Tinctura Gelsemii (U.S.P.).—15%. Alcohol. (B.P. = 10%. Two-thirds alcohol.) *Dose:* 1 to 4 c.c. (¼ to 1 drachm).

* *Gelseminin.—Dose:* 0.0005 to 0.002 Gm.

Lobelia (U.S.P., B.P.).—(*Indian Tobacco.*) Leaves and tops of *Lobelia inflata* (collected after a portion of the capsules has become inflated), Lobeliaceæ. North America.

Lobelin.

Extractum Lobeliæ Fluidum (U.S.P.).—One-half alcohol. *Dose:* 0.05 to 0.5 c.c. (1 to 10 minims).

Tinctura Lobeliæ (U.S.P.).—20%. One-half alcohol. *Dose:* 0.3 to 2 c.c. (5 to 30 minims).

Tinctura Lobeliæ Ætherea (B.P.).—20% in spirit of ether. *Dose:* 0.3 to 2 c.c. (5 to 30 minims).

Scoparius (U.S.P.) [**Scoparii Cacumina**, B.P.].—(*Broom Top.*) The tops of *Cytisus Scoparius*, Leguminosæ. Western Asia and Southern Europe; naturalized.

Spartein, Scoparin, Tannic Acid.

⁂ *Extractum Scoparii Fluidum* (U.S.P.).—One-half alcohol. *Dose:* 1 to 4 c.c. (15 to 60 minims).

* Not official.

The most important preparations are marked ⁂.

** The free alkaloid is liquid.

⁂ *Sparteinæ Sulphas* (U.S.P.). ** —*Dose:* 0.006 to 0.12 Gm. (1/10 to 2 grs.).

⁂ *Infusum Scoparii* (B.P.).—10%. *Dose:* 30 to 60 c.c. (1 to 2 ozs.).

Succus Scoparii (B.P.).—3% of the juice. *Dose:* 4 to 8 c.c. (1 to 2 drachms).

Physostigma (U.S.P.) [**Physostigmatis Semina**, B.P.].—(*Calabar Bean.*) The seed of *Physostigma Venenosum*, Leguminosæ. Tropical Western Africa.

Physostigmin, Eseridin, Calabarin.

Eseridin has an action similar to Physostigmin, but weaker. Calabarin belongs to the Strychnin group

The liquid preparations spoil very rapidly and are unreliable unless freshly made.

Extractum Physostigmatis (U.S.P., B.P.).—Alcohol. *Dose:* 0.006 to 0.03 Gm. (1/10 to 1/2 grain).

Tinctura Physostigmatis (U.S.P.).—5%. Alcohol. *Dose:* 0.6 to 2 c.c. (10 to 30 minims).

Physostigminæ (Eserinæ) *Sulphas* (U.S.P., B.P.).

⁂ *Physostigminæ Salicylas* (U.S.P.) —Soluble in 150 water, 12 alcohol. *Dose:* 0.0005 to 0.002 Gm. (1/100 to 1/30 grain). For use in eye: 1% solution.

Lamellæ Physostigminæ (B.P.).—Each, 1/1000 grain.

CHAPTER XIII.

INTERNAL SECRETIONS.

INTERNAL secretions may be defined as specific substances formed within a glandular organ and given off to the blood or lymph. (Howell.)

Historical.—The introduction of these principles into medical practice may be considered one of the valuable achievements of modern therapeutics, only equaled by the antitoxin treatment, which is in some ways similar to it.

Organtherapy might at first view be mistaken for a reversion to the customs of the savage who ate the heart of his courageous enemy to magnify his own prowess. Indeed, stimulated by the undoubted achievements of scientific organotherapy, there has recently been introduced an era of indiscriminate employment of organ extracts against the diseases of the corresponding organs,—partly by people who have an honest desire to advance knowledge, but lack the scientific training to comprehend the requirements of this treatment, partly by quacks who simply take advantage of the prevailing fashion. Such pseudo-discoveries do not depart in their spirit from the above-mentioned symbolism, and their fate is easy to predict. They have nothing whatever to do with the scientific theory and use of internal secretions as deduced from experimental data. (How great is the danger in this field is illustrated by a certain prostatic extract put out by manufacturers for the treatment of prostatic hypertrophy. It gave the most brilliant results until investigation brought to light the fact that it had been gained from female animals.)

Our knowledge of this subject was started by Claude Bernard's discovery

The most important preparations are marked ⁂.

** The free alkaloid is liquid.

of the glycogenic function of the liver. Brown-Séquard, basing himself upon this mainly, advanced the brilliant theory of what he was the first to call "internal secretion," of its important functions to the organism, and suggested it as a possible new field in therapeutics. Séquard demonstrated none of these secretions, much less their passage into blood and lymph. Since that time great advance has been made along this line. Internal secretions have been demonstrated in glands with and without ducts. Fatal effects of excision of some of these organs—*e. g.*, the thyroid—first served to direct attention to their secretory function. Further investigations constated that the extracts of these glands possessed specific physiologic properties. The latter correspond for the most part to those of members of the series comprised in this treatise between the extremes of atropin and physostigmin.

The **nature of the active substances** is none too well known. However, they differ from proteids and from toxins in being resistant to heat and reagents. Although not themselves proteid, they may form a constituent part of a complicated proteid molecule. They are, perhaps, more nearly allied to the alkaloids. Some, in fact, are typical alkaloidal bases (epinephrin), while others belong to the pyridin series (suprarenin).

It is of interest, as throwing some light on the origin of these bodies, to note that albumin, under the influence of concentrated hydrochloric acid, yields a small quantity of pyridin bases.

Manner of Action.—There has been considerable discussion as to whether the function of these substances is antitoxic or physiologic—*i. e.*, whether they are chemically or functionally active.

They certainly are the latter, for their physiologic activity is easily demonstrated by injection or feeding. As to the former—the chemic destruction of poisons by them—very little is known. However, some of them favor oxidation, which is undoubtedly a normal aid in the removal of poisons. Such chemic and oxidative action is also rendered very probable by the fact that blood of animals from whom the glands have been excised is toxic to other animals, especially when the glands from these have also been removed. But even this is not decisive, for it still remains to be shown whether it is the gland itself or its products which possesses the antitoxic action.

These glands appear to vary considerably in their activity at different ages. Thus, the thyroids are more active in children, almost inactive in old people. The activity of the gland appears comparatively early in the embryonic life, the order varying somewhat in different genera: In the human embryo, first in the thymus, then the thyroid, and lastly the suprarenal. At birth, the thyroid is devoid of iodin.

The bad effects following the excision of these glands can in all cases be removed if the gland substance is administered. This is usually active when given by the mouth, which constitutes a very marked difference from antitoxins. The latter are typical proteid bodies (globulins), and are destroyed in the stomach.

In therapeutics, the fresh or dried gland substance, or extracts made from it by means of glycerin or normal salt solution, are still employed. The active principles cannot as yet be isolated with sufficient accuracy to allow of their use. In the preparation of these extracts, etc., asepsis must be enforced with extreme care.

I. SUPRARENALS.

Suprarenal extracts are only active on intravenous injection or when applied locally. Subcutaneously they have no effect, except in very large and often fatal doses.[1] This is on account of the oxidation of the suprarenin in the tissues. Taken by the mouth they are absorbed, and produce only local and perhaps reflex effects. On the whole, their action resembles that of piperidin.

(A) SUMMARY OF ACTIONS.

1. Rise of blood pressure through peripheral stimulation of the vasoconstrictor mechanism. Secondary to this rise of pressure there is a stimulation of the vagus and, consequently, a slowing of the heart.
2. A digitalis action on the heart.
3. A depression of the respiratory center.
4. A veratrin action on the muscles.
5. A diminution of peristalsis through peripheral action on the nervous mechanism.
6. Mydriasis through direct stimulation of the iris musculature.

(B) DETAILS OF ACTIONS.

1. Rise in Blood Pressure.—This appears after extirpation of the cord, and is therefore peripheral.

The same is shown by perfusion of excised organs. It cannot be considered as definitely settled whether the action is upon the muscle or nerve endings.

The action upon the *vessels of the brain or lungs* is uncertain. The bulk of evidence goes to show that there is none, or at least very little, and this points to the action being upon the *nerve endings*.

The vasoconstriction is manifested especially in the *splanchnic area*. It is but slight on the *vessels of the skin*.

With the *renal vessels* the constriction is but transitory and is followed by dilatation. The flow of urine is successively diminished and increased.

The rise in the general blood pressure is ordinarily very large, but is to a great extent counteracted **by slowing of**

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[1] Very large hypodermic doses show ascending central paralysis, hemorrhage from mouth and nose, hematuria, occasionally convulsions, great fall of temperature, all these being probably secondary to the changes in blood pressure.

the heart. This is due to a stimulation of the vagus center secondary to the rise of blood pressure, for it occurs only after this has begun. It is not invariably found.

2. The action upon the **isolated heart** is primarily that of digitalis.

In the *frog's heart* it first increases the amplitude and rate. The output is increased per beat and per time. The heart then assumes a more and more systolic phase, becomes more and more slowed, and is arrested in systole.

The *mammalian heart* shows the same phenomena.

Langendorff's method shows a *strong and persistent increase in the tone* (passage toward systole). (Fig. 57.)

Porter's method shows that the *height of the contraction is much increased*, the tone doubled. Large doses should, as with digitalis, cause *fibrillary contractions.*

Hering's method shows *quickening of the beat* and *rise of blood pressure.*

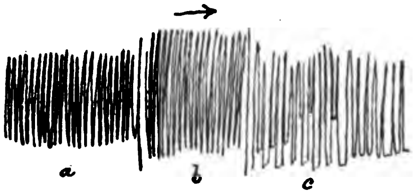

Fig. 57.—Suprarenal extract on isolated heart (after Hedbom): *a*, Normal; *b*, four minutes after injection; *c*, five to six minutes.

From this it will be seen that its action is *beyond the ganglia* and results in an increased rate, increased excursion, increased volume of blood, then an increased systolic tone, and finally fibrillary contractions or systolic standstill.

The increase of tone seen at the beginning of its action in *intact animals* is followed by slowing and tendency to diastolic phase due to vagus stimulation.

3 and 4 do not require further discussion.

5. **Effect on Peristalsis.**—Peristalsis is markedly lessened. Since this effect appears after division of the splanchnics, it is peripheral. This is so different from its action on the muscular organs that one must assume it to be due to an action on some *nervous* mechanism, the stimulation of some nerve endings, or of Auerbach's plexus.

It has no effect on nerve-trunks or nerve endings.

(C) RELATION TO OTHER DRUGS.

Its action resembles that of a number of other groups:

1. **Piperidin** in the rise of blood pressure. The difference lies in the respiration, which is quickened and deepened by piperidin.[1]

2. **Pyrocatechin,** which has the same general action as piperidin, but is much more toxic.

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[1] Piperidin differs from coniin mainly in somewhat weaker curare action.

3. **Nicotin** in its action on the circulation.
4. **Digitalis** in its action on the heart.
5. **Veratrin** in its action on the muscles.

It is at the same time antidotal to toxic doses of nicotin, atropin, neurin, strophanthin.

(D) NATURE OF THE ACTIVE CONSTITUENTS.

The *active constituents* are contained almost exclusively in the medulla of the gland.

The latter is indeed possibly a physiologically different organ from the cortex. (In certain fishes the cortex and medulla exist in two separate glands.)

Two substances have been isolated by different observers: epinephrin by Abel, and suprarenin by von Fuerth.

Epinephrin is a typical alkaloid possessing basic characters. **Suprarenin** is very similar to, but not identical with, pyrocatechin; it is probably di- or tetrahydrodioxypyridin.

Neither of these has so far been made synthetically, which would seem to be the next step in this interesting subject. Suprarenin forms about 0.1 to 0.17% of the gland. Both observers acknowledge the presence of both bodies, but each claims that the results obtained by the other are due to admixture of his own substance. The bulk of evidence seems to be in favor of von Fuerth.

The activity of the substance is very great. Even in such impure form as it exists in the medulla of the gland, 0.55 mg. per kilo of dog has a maximal effect. The action is very short, and the animal soon returns to normal.[1] However, the substance is not eliminated by the kidneys.

It must, therefore, be destroyed in the tissues, and this by oxidation, for alkaline solutions are oxidized quite readily in the presence of air, and thus rendered inactive. This destruction takes place comparatively slowly in the blood, but especially strongly in the tissues and in the liver. This explains why hypodermic injections are so ineffectual.

On the other hand, the substance is quite *resistant against acids and heat.* It can be boiled without destroying its action. It is soluble in water and fairly strong alcohol, and does not reduce copper.

As it belongs to the piperidin series, it contains nitrogen.

(E) EFFECTS OF EXCISION.

Animals die soon after excision of the suprarenals (five days with the cat), usually showing a low blood pressure and muscular weakness. Alterations are also seen in the central nervous system and in metabolism. Death occurs by failure of respiration.

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[1] Large doses often repeated, kill by cardiac paralysis.

This cannot be taken to prove positively the importance of the suprarenal glands on account of the extensive nervous connections involved in the operation.

In advanced Addison's disease the glands are almost inactive. In the human fetus they are inactive at the time of birth.

A complementary proof of the functional importance of these glands is furnished by the injection into normal animals of the blood of animals in whom the glands have been removed. This produces curare-like symptoms, which are improved by suprarenin.

The *function* of the suprarenals is probably the destruction of the muscle waste-products (skeletal, cardiac, and vascular) and their conversion into substances of an opposite action—*i. e.*, stimulants to the muscles. The function is, therefore, both chemic and physiologic.

That the active substance is actually excreted by the glands into the blood is shown by the fact that the blood of the suprarenal vein produces the typical effect. The substance is carried in the plasma, not the corpuscles.

(F) THERAPEUTICS.

The therapeutic results from the suprarenal extract must necessarily be small when one considers that its action is short and that it is totally inactive except when injected intravenously. Its results in Addison's disease, rickets, diabetes insipidus, and other diseases in which it has been employed, have been so doubtful that one might call them negative.

On the other hand, it has proved very useful as a *local application* to stop hemorrhage, especially in nasal and laryngeal operations. It is then usually applied in 6% of solution of the dried gland in conjunction with cocain, Chewing of suprarenal tablets is stated to arrest nasal, pulmonary, and gastric hemorrhage.

Some Commercial Preparations:

⁂ *Extractum Suprarenale hæmostaticum* (Merck). Dry, for local use in 6% solution.

⁂ *Tablets* (Burroughs, Welcome & Co.) are said to be especially active.

* *Suprarenin.*

* *Glandulæ Suprarenale Sicc. Pulv.* One part = 5 of fresh gland. *Dose:* 0.2 Gm.

* Not official.

The most important preparations are marked ⁂.

II. THYROID.

The importance of this gland appears most conspicuous from the symptoms which arise when it is excised.

I. EFFECTS OF THYROIDECTOMY.

Schiff, in 1856, was the first to show the fatal sequence of thyroidectomy in animals.

The symptoms differ considerably in *different animals*, in the rapidity of development as well as in violence. In birds the operation is not followed by any effects. The age of animals has also considerable influence, the symptoms being much less violent in old age, much more marked in children and young animals.

Acute Symptoms.—In the acute form (*e. g.*, dogs) the symptoms consist in an exaggeration of the reflex excitability, which increases to choreic spasms (tetany), and later to intermittent convulsions. The animal becomes apathetic and cachectic, the cutaneous sensibility is diminished, the animal manifests a very marked desire for external heat, the body temperature is lowered (due to increased heat loss through a diminished power of regulating its temperature). The number of red corpuscles is diminished, as is also the hemoglobin in the same ratio. The proteids of the serum are also lessened. Death occurs after a few days.

The *convulsions* have their *seat* in the central nervous system, for they disappear on section of the motor nerves. They persist, however, on removal of the corresponding motor area, so that they must be located somewhere between this and the nerve-trunk.

Slow Form.—In animals in which the development of the symptoms is slower, as in man and the monkey, these symptoms are preceded by a more marked cachectic and *cretinic condition*, and furthermore by a peculiar change in the skin—*myxedema.* This consists of a hyperplasia of the connective tissue with reversion to the embryonic type, and consequently a richness in mucus. These symptoms are not seen in the dog, since there is not time for their development.

A certain proportion of dogs do not show much change after thyroidectomy. It is found in all these cases that the animal possesses *accessory thyroids*. These may be situated in various places, often in the neck or near the arch of the aorta, and possess the same structure as the thyroid gland. They hypertrophy after removal of the latter.

Rabbits do not die after removal of the thyroids. However, if certain small glandular bodies lying in the neighborhood of the thyroids—*parathyroids*—are also removed, the animal dies very quickly. In the dog these bodies are situated inside the thyroid gland and are, therefore, removed in the ordinary operation. If they are spared, the dog also survives more frequently. The removal of these bodies alone in either animal causes death with symptoms similar to those of thyroidectomy. It is possible, however, that their functions are distinct, although similar.

They have also been demonstrated in the sheep, seal, monkey, man, and exist probably in all animals.

2. THYROID FEEDING AFTER THYROIDECTOMY.

The above symptoms may be entirely prevented by leaving a portion of the gland or by transplanting it into any portion of the body, or in man even by feeding with gland substance.

(This thyroid feeding was first tried in 1884.) In dogs and monkeys thyroid feeding is not so uniformly successful, but it saves a certain proportion of these animals also.

The same results follow the administration of the active principle—iodothyrin.

3. THE EFFECT OF INJECTION OF THYROID ON NORMAL ANIMALS.

Summary of Actions (when large doses are injected intravenously):

(1) A fall of blood pressure through vasomotor dilatation and depression of the cardiac muscle.

(2) Slight action on the heart muscle: small doses increase, large doses diminish, its force.

(3) Increase of the irritability of the vagus endings in the heart.

Details of these Actions:

(1) **Fall of Blood Pressure.**—Since this is developed independently of any cardiac action, it must be vasomotor in its origin, but it is not known whether it is central or peripheral.

(2) **Heart.**—The effects are small, and have been overlooked by most observers, but when observed they have been fairly uniform. Since they occur on Porter's preparations, they must be muscular. It also renders the heart beat more regular.

(3) **Vagus Endings.**—The effect antagonizes atropin.

(4) Quickening of the heart from stimulation of the accelerator center. (This is also seen when thyroid is administered to myxedemic patients. Rabbits show a slowing.)

4. EFFECTS OF CONTINUED ADMINISTRATION OF SMALLER DOSES.

The effects of the continued administration of smaller doses (such as are seen when overdoses of the substance are taken in the treatment) are somewhat different.

They resemble *Basedow's disease.* (This is now regarded as due to excessive secretion of the thyroid. Histologically the secreting surface is seen to be increased by extension of the papillæ in the lumen of the alveoli.)

The *symptoms* are partly nervous, partly circulatory. The former consists in insomnia, headache, palpitation, nausea, vertigo, polyphagia or loss of appetite, diarrhea, general malaise, tremors of extremities. The heart's action is irregular and exaggerated, and there are also various vasomotor disturbances.

Effects on Metabolism.—Oxidation is markedly increased, and both nitrogenous and non-nitrogenous bodies are rapidly used up. The temperature rises. However, and in whatever conditions, thyroid is administered, it causes a large increase of N in the urine, but the first effects are upon fat, and it acts upon proteids only when the former have been reduced to a certain minimum. The quantity of urine is also increased.

Since arsenic retards oxygenation, its use has been suggested to combat this side-effect of the thyroids, and good results have been claimed, but are scarcely sufficiently established.

5. FUNCTIONS OF THE THYROIDS.

The physiologic action of the injection of thyroid extract —the fall of blood pressure and the increase of the irritability of the vagus endings—renders it probable that the gland has an important connection with the *circulation.* Moreover, the gland itself contains powerful vasodilator fibers which can greatly lower the pressure in the carotid.

Its situation would render it most favorable for influencing the circulation of the *brain*, and indeed nothing prevents the attributing to circulatory changes in the nervous centers all the nervous symptoms following the injection or excision. But it would be going rather far to explain its action on *metabolism* on the same basis. This function is not understood. In addition, some experimenters claim a certain *antitoxic action.* Caffein is said to be more toxic in animals deprived of thyroids. The blood of thyroidectomized animals was claimed to be toxic to others from whom these glands have just been removed, but this is now denied.

6. ACTIVE PRINCIPLES.

Thyroid glands differ from the suprarenals in that they exert their action when taken by the mouth. Indeed, Baumann has isolated a substance, very rich in iodin (9.3 %),[1] resistant to heat and even to concentrated acids, which possesses all the physiologic properties of the gland extract, and which he calls "*iodothyrin.*" It also contains nitrogen and phosphorus. It does not give the biuret or Millon's reaction.

The thyroid of the newborn child does not usually contain iodin, but this is found in the accessory and para-thyroids. None exists in the thymus.

In the gland the active substance is confined to the colloid and probably exists in combination with globulin as *thyreoglobulin* (1.66 % I). The colloid does *not* contain mucin. The amount of iodothyrin can be increased by the administration of KI, but the direct iodization of this substance outside of the body results in the destruction of its physiologic activity.

It can be diminished by an exclusive meat diet. The iodin administered as iodothyrin, etc., is not excreted at once. The colloid is secreted into the lumen of the alveoli by the epithelial cells, which may or may not undergo destruction in this process. It is discharged from here into the lymph, usually by rupture of the alveolar walls. The vacuoles existing in the colloid are probably artifacts. Pilocarpin does not increase the colloid secretion.

7. RELATION TO OTHER GROUPS.

The large proportion of *iodin* in iodothyrin might lead to the thought that perhaps the iodin itself had a similar action. This is far from being the case, for the action of the latter or of iodids in intravenous injection is precisely the opposite: The excitability of the vagus fibers is diminished, and the effect of thyroid injection is abolished, while the blood pressure is raised.

Sodium phosphate, on the other hand, has the same action on vagus endings as iodothyrin.

These are, therefore, two antagonistic groups: (*a*) Iodothyrin and sodium phosphate increase the excitability of the vagus and depressor endings and cause a fall of blood pressure. (*b*) Iodin and atropin diminish the excitability of the vagus and cause a rise of blood pressure. Thyroiodin would, therefore, come *nearest to the muscarin group.*

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[1] By starting from thyreoglobulin, Oswald has obtained iodothyrin of 14.3% I.

8. THERAPEUTICS.

(a) **Conditions in which the Functions of the Thyroid Gland is Evidently Defective.**—In these the benefit persists only so long as the administration is continued.

Cachexia strumipriva.

Goiter.—The form of goiter which is most conspicuously influenced is hyperplastic follicular. Complete disappearance is the exception, but considerable decrease the rule, especially in young patients. Results are not permanent, and usually there is a relapse if the remedy is discontinued.

Myxedema.

Sporadic Cretinism.

(b) More obscure are its actions, if indeed they exist, in various **skin diseases**: psoriasis, eczema, lupus. Also very obscure are the reported benefits to **uterine fibromata.**

(c) **Obesity.**—Since in these cases the object is to reduce the fat and not the muscle, and since thyroid increases the metabolism in both, it must be joined with an abundant proteid diet, nor should its administration be continued a very long time.

(d) Since it has been observed that thyroidectomy retards the growth of bone and the formation of callus after fracture, the administration of thyroid has been suggested for **slow-healing fractures.** It has not been sufficiently tried to allow definite conclusions.

(e) Thyroid administration has been suggested for chronic rheumatism, gout, arteriosclerosis, rickets, infantile cachexias, etc. It is doubtful whether it is of any real benefit in these conditions.

9. SOME COMMERCIAL PREPARATIONS.

* *Fresh Sheep's Thyroid*, preferably raw or broiled. 1/8 to 1/3 gland as dose.

* *Thyroid Tablets.*

Thyroideum Siccum (B.P.).—The dried gland of the sheep = 6 parts of fresh. *Dose:* 0.3 to 0.6 Gm. (2 to 10 grs.).

Liquor Thyroidei (B.P.).—100 minims = one gland. *Dose:* 0.3 to 1 c.c. (5 to 15 minims).

* *Iodothyrin* (Thyro-iodin).—The commercial preparation is a milk-sugar trituration, containing 0.03% I (instead of 9.3%). Its *dose* is 1 to 2 Gm. per day.

III. PITUITARY BODY (HYPOPHYSIS CEREBRI).

Injections of extracts prepared from the hypophysis proper—*i. e.*, the portion of the gland which possesses a structure resembling the thyroid—have very little effect beyond a slight rise of blood pressure. The active part of the gland is the *posterior portion*—the infundibular body. The effects of injection of extracts made from this may be *summarized* as follows:

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* Not official.

1. *Vasoconstriction* with rise of blood pressure.
2. *Stimulation of the vagus center and increased irritability of the vagus endings* (an action antagonistic to atropin).
3. *Digitalis action* on the cardiac muscle (Porter's preparation), consisting of a slowing with increasing tonus. The amplitude is first increased, then lessened.

The effect of different extracts is quite variable in the predominance of the cardiac and vasomotor actions respectively. Cyon, therefore, assumes *two separate bodies*, the first (hypophysin) acting on the heart, the second on the blood pressure.

Aside from its secretions, the hypophysis seems also to control the circulation in the same sense through nervous connections. Indeed, it seems to form an *essential link in the chain for reflex stimulation of the vagus center:* Cyon obtained by electric or mechanical stimulation of the gland a slowing of the heart which is abolished on section of the vagi. The usual reflexes giving rise to vagus stimulation, rise of blood pressure, inhalation of ammonia by rabbits, etc., do not occur when the hypophysis is destroyed. Although this seems to be a link in the normal path, it is not an indispensable factor in these reflexes; for in many animals it is entirely atrophied and does not respond to stimulation and its secretion is inactive.

Cyon assumes its *functions to be the regulation of the blood-supply of the brain* through the general circulation. Since it is exposed to the same conditions as the brain itself, a rise in the intracranial pressure will stimulate it mechanically, and this will cause a slowing of the heart and, consequently, a tendency to lowering of the pressure. These nervous functions are supported by its chemic secretions.

In this way it is able to *supplement or replace the effect of iodothyrin* on the heart, although it acts through an entirely different mechanism—*i. e.*, centrally.

The *effects of excision* of the gland resemble those of thyroidectomy, pointing to the importance of both to the circulation of the brain. These symptoms are usually relieved by injections of the extracts.

The gland is usually found atrophied in *acromegaly*, a condition of gigantic overdevelopment of the extremities, skull, tongue, nasal mucous membranes, etc., and by various visual disturbances; but a causal connection between these two cannot be considered as definitely proved. Nor have results of its therapeutic use in this disease been at all encouraging. The dried extract is used in doses of about 0.1 Gm.

IV. THYMUS.

Experiments with this gland have not yet led to any very striking results. This might have been predicted from its histologic structure, since it consists exclusively of lymphoid cells. The same holds of the spleen.

On account of their contents of nucleins, they are said to *stimulate the production of blood-corpuscles*. They, as well as bone-marrow, have been tried in rickets, anemia, chlorosis, and leukemia, but without great success. The various extracts may be used.

These nucleins have of recent years been extensively tried for various obscure affections, and so far it is impossible to say anything definite about them. They are converted into xanthin bodies in the organisms. They are rich in phosphorus and are not destroyed by peptic digestion. Under the action of alkalies they are split into an albumin and into *nucleic acid*, which latter retains the phosphorus. It is used in hemophilia (as also nuclein), and as a mild caustic. (It is claimed that it destroys diseased tissue, but leaves healthy tissue intact.) *Nuclein* is made either from yeast or from spleen. It occurs as a powder, soluble in weak alkalies. It is given by mouth in daily doses of 2 to 3 Gm. or subcutaneously as 1 c.c. of 0.5% solution.

Yeast has recently been recommended (by mouth and locally) against furunculosis. More extended observation is needed to establish its value.

V. PANCREAS.

Although this gland has for its most conspicuous function an external secretion, its internal secretion is none the less important. Its removal leads to *glycosuria*, with acetonuria, polyuria, great thirst and hunger; in fact, conditions closely analogous to diabetes mellitus. This glycosuria occurs even when carbohydrates are withheld.

It can scarcely be considered as decided whether these effects are due to the absence of some substances produced in the pancreas or whether the cells of this organ are themselves necessary to the normal carbohydrate metabolism.

While it does not seem improbable that some cases of *diabetes* in man are connected with disease of the pancreas, it must be confessed that administration of the powdered substance or extract has not been therapeutically successful in these conditions.

VI. PHLORIDZIN.

This is a glucosid found in the root bark of the apple- and other trees. Its administration produces effects which superficially resemble excision of the pancreas. The most marked of these are *glycosuria and acetonuria*, and a *great increase in the nitrogen metabolism* (as much as six times the normal).

The action is, however, really very different. It affects primarily not the metabolism, but only the *epithelium of the kidneys*, rendering this *more permeable* to sugar. In this way the sugar leaves the blood and body very rapidly. As long as the stored carbohydrates of the body are sufficient to make up for this loss, the proteids are not affected, but later these are decomposed by the splitting off of the carbohydrate molecule. The dextrose and nitrogen in urine, then, always present a definite relation (3.75 D : 1 N).[1]

As to *acetonuria*, this seems to result in all forms of faulty carbohydrate metabolism; especially in any condition in which an insufficient amount of carbohydrates is burned. Such a condition may result, as in the present case, from an abnormal drain, or it may be the result of diminished capacity for using the sugar, as in pancreatic diabetes; or of an insufficient supply, as in carbohydrate-free diet. Since the acetone and oxybutyric acid which always accompany it form the dangerous element in the diabetic coma, it will be clear how the reduction of the carbohydrates in the diet below a certain limit will become detrimental. (See p. 220.)

Acetone is also increased by an excessive amount of fat in the food, being probably at least in part formed from the fatty acids.

Like all those drugs which effect a large increase in the nitrogen metabolism, phloridzin causes a fatty infiltration of the liver.

VII. KIDNEYS.

Even this organ, whose function is so conspicuously connected with external secretion, appears also to be charged with the function of internal secretion. This action is largely *metabolic*; removal of a large portion of the kidney increases the proteid waste of the body. It cannot be stated whether this is connected with a chemic substance.

Kidney extracts also have some action on the *circulation*. The effect on the isolated heart-muscle is comparatively small. It consists in lessened tonus, slight slowing, and increased amplitude. The blood pressure falls at first, then rises. These effects are not due to urea, which causes in the isolated heart a slight increase in the tonus, with some acceleration, and slight increase of force.

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[1] Some recent experimenters claim that the proteid destruction is only secondary to a fat destruction, and that the sugar is derived from the latter; also, that the ratio D : N may fall as low as 2.8 : 1.

VIII. SEXUAL GLANDS.

Extirpation of the sexual glands was amongst the earliest surgical operations, and thus it could not fail to be noticed that it is followed by very marked psychic and physical changes. But the subject was neglected therapeutically until the announcement by Brown-Séquard, in 1889, of the remarkable stimulating qualities which he noticed on hypodermic injection of orchitic extract.

This discovery was exploited in so sensational a manner that the whole subject was in danger of falling into discredit. While the somewhat extravagant claims of the discoverer must be considerably discounted, numerous independent observers have shown by the ergograph that it causes a marked *increase* (15% to 20%) *of power for voluntary muscular work.*

This action has been attributed by Poehl to the base *spermin* ($C_5H_{14}N_2$). While this is especially abundant in this extract, it also exists in many other tissues. Its actions on the heart and circulation resemble those of *cholin*, which is also present in the orchitic extract. Its phosphate forms the "*Charcot-Leyden*" crystals found in sputa, etc. The action of these substances is supported by a nucleoproteid, which causes a slowed heart and fall of blood pressure through stimulation of the vagus center, and dilatation of the splanchnic vessels, also through the center. The orchitic extract applied to the *isolated heart* (Porter and Langendorff method) shows increase in force and frequency.

Much more conspicuous, however, are the effects of the sexual glands upon **metabolism.** This was first observed clinically: After the climacteric or oöphorectomy, *obesity* occurs in about 40% of the cases. The excision of the testicles has much less effect. In addition to this increase of fat, the loss of the ovaries also brings with it a very characteristic train of phenomena, generally attributable to spasms of the vascular system.

The subject has recently been studied experimentally on bitches by measuring the heat production. A very marked decrease of this is found after the operation—*i. e.*, oxidation, and consequently carbon and hydrogen metabolism, are diminished.

This effect is abolished by administration of ovarian extracts by the mouth. In other words, ovarian substance *increases oxidation with the castrated animal*, even somewhat above the normal amount. On the normal animal, on the other hand, it has no such effect.

Males show exactly the same phenomena, but much less marked. The spermatic extract has the same action as the ovarian on both sexes, but the ovarian is much more powerful.

The metabolic function of the ovaries is to some extent supplemented by the uterus. The diminution of heat-production does not reach its maximum until the uterus has undergone atrophy.

Administration of ovarian substance does not prevent atrophy of the uterus after excision of the ovary.

Therapeutically, ovarian tablets have been found quite successful in all the conditions following the functional loss of the ovaries. They have also been tried in chlorosis, but without decided benefit.

Extracts of the **mammary** and **parotid** glands have also been tried against uterine fibroids, but the beneficial results which have been reported can scarcely be accepted until further confirmation.

MATERIA MEDICA.

Testicular Extracts (from Bull or Ram):

* *Testes Siccati Pulv.*, *Didymin*, *Testin*, *Testis*.—Dry glands or extracts. *Dose:* 1 Gm.

* *Spermin Poehl.*—1 to 6 c.c. of 2% solution, hypodermic.

* *Succus e Testibus.*—Liquid preparation, 15 c.c.

Ovarian Extracts (Cow or Swine):

* *Oöphorin.*—A dry extract, ten times as strong as fresh ovaries. *Dose:* 1 to 2 Gm.

* *Ovariinum Siccum.*—Five times as strong as fresh glands.

* Not official.

CHAPTER XIV.

APOMORPHIN; EMETIN; EMETICS.

(A) APOMORPHIN.

This is a base formed by *dehydrating morphin* through the action of concentrated mineral acids:

$$\underset{\text{Morphin.}}{C_{17}H_{19}NO_3} - H_2O = \underset{\text{Apomorphin.}}{C_{17}H_{17}NO_2}$$

It has *lost almost all the narcotic action* of morphin and shows a further development of the excitant effects which were noted in the action of the former on certain animals (see p. 199). It shows in addition a depressing action on striped and cardiac muscle.

I. SUMMARY OF ACTIONS.

1. Irritation of the central nervous system, and particularly of the vomiting center in the medulla.
2. Depression of striped and cardiac muscle.

II. DETAILS OF ACTION.

1. **The irritation of the central nervous system** is shown first and mainly upon the **vomiting center**, its action being so specialized that small doses give rise purely to the symptoms of emesis without developing any other direct action.

The vomiting is preceded by the classic **symptoms of nausea**, which must not be ascribed to a direct action of the drug. They are: a feeling of sickness, lassitude and weakness, increased secretion of sweat, saliva, mucus, and tears, a sensation of warmth. *During the act* of vomiting there is also an increase of respiration and pulse, and of blood pressure.

The nausea symptoms are also obtained from doses too small to produce vomiting (1 to 2 mg. every two hours by mouth).

With the usual hypodermic dose (5 to 10 mg.—$\frac{1}{12}$ to $\frac{1}{6}$

grain) vomiting occurs in man usually inside of *fifteen minutes*, and the nausea usually disappears very quickly; it may, however, persist for some time and the vomiting be repeated. Even *collapse* may occur, simply as the result of the vomiting, and not as a direct effect. It is not dangerous.

The vomiting with apomorphin is mainly of *central origin.*

The fact that it occurs more quickly and with a smaller dose if the drug is administered hypodermically than when it is given by stomach would point to this. And even more direct proof can be furnished: After the blood-vessels supplying the stomach have been ligatured, apomorphin produces no effect when placed in this organ, but acts when injected into the general circulation (from which it cannot reach the stomach). Its central action is, however, supported very slightly by a *local* one, since it causes weak contraction in the excised stomach; but this plays a very subordinate rôle.

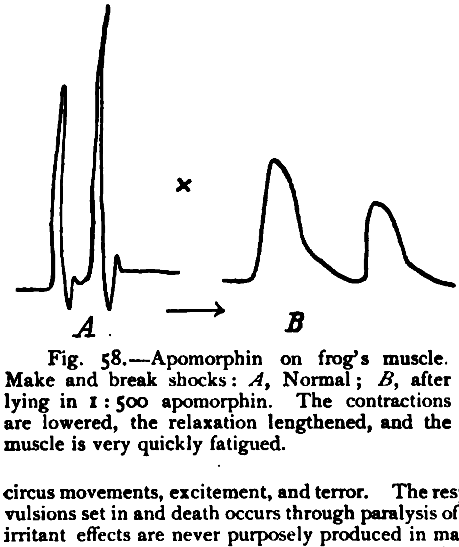

Fig. 58.—Apomorphin on frog's muscle. Make and break shocks: *A*, Normal; *B*, after lying in 1 : 500 apomorphin. The contractions are lowered, the relaxation lengthened, and the muscle is very quickly fatigued.

2. If the drug is taken in *very large doses*,—and especially by **animals which are incapable of vomiting**,[1]—it exhibits its irritant effects upon the rest of the central nervous system. It causes great restlessness with circus movements, excitement, and terror. The respiration is quickened. Convulsions set in and death occurs through paralysis of respiration. These general irritant effects are never purposely produced in man, and are rarely witnessed. Very minute doses (up to 2 mg. in man) are slightly hypnotic.

3. The irritability of **striped muscle** is much diminished and finally abolished by it in frogs (Fig. 58), but this action has not been shown in *mammals*: the muscular weakness witnessed in the latter depends purely upon the nausea.

4. A similar action is shown on the **cardiac muscle**: it stops the heart even after atropin (see p. 294).

5. It paralyzes nerve-cells and ganglia on direct application.

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[1] Fish, frog, toad, and lizard vomit easily in certain seasons (June and July best, January and February worst), and stomach must be filled with food. All birds vomit, but from the crop, and not from the stomach. Hogs vomit with difficulty. Other animals with paired hoofs, insect-eaters and carnivorous, vomit easily. Animals with odd hoofs, ruminants, and rodents cannot vomit, although large doses of emetics may cause salivation and nausea. It is well known that young children vomit very much more easily than adults.

III. TOXICOLOGY.

The toxicology of apomorphin is not important. It is not *excreted* into the stomach like morphin, but is probably decomposed in the organism.

Quebrachin, *aspidosamin*, *quebrachamin*, and *aspidospermin* have a similar action, but vomiting is not so prominent a symptom.

IV. MATERIA MEDICA.

⁂ **Apomorphinæ Hydrochloras** (U.S.P., B.P.).—Grayish powder, quite soluble in water. As an emetic, 5 to 10 mg. are given hypodermically in 1% solution. As an expectorant, 2 mg. per mouth. The solutions become *green* in the light, but this change does not greatly lessen their activity.

Injectio Apomorphinæ Hypodermica (B.P.).—1%. (To be freshly prepared.) *Dose:* 0.3 to 0.6 c.c. (1 to 10 minims).

Therapeutics, see page 326.

Oxydimorphin (see p. 212) is another morphin derivative with a somewhat similar action: Weakening of heart and circulation; later, degenerations; increased peristalsis; central vasomotor paralysis; death through respiratory standstill. The resemblance of these to the "withdrawal" symptoms of opiumism is quite remote, nor are the two antidotal, as was formerly claimed.

(B) EMETIN (IPECAC).

I. ORIGIN.

Emetin was until recently supposed to be a single alkaloid, but at present is shown to consist of two bases (cephælin and emetin) of nearly identical action. It is the active principle of ipecac, and perhaps also of some other emetic drugs; but it is always employed in practice in the form of galenic preparations of ipecac.

Its actions bear a general resemblance to those of apomorphin, but with important points of difference, especially a stronger local action.

Triosteum (Fever-wort, Caprifoliaceæ; North America) also seems to belong to this group.

II. SUMMARY OF ACTION.

1. A strong local irritant effect, exerted particularly on the alimentary canal, resulting in vomiting and diarrhea.
2. Excitation with following paralysis of the central nervous system.
3. A weak apomorphin action on striped and cardiac muscle.

III. DETAILS OF ACTION.

The phenomena of **vomiting** and nausea are the first and most prominent symptoms, and present the clinical picture described under apomorphin (p. 321). This action is probably both central and local. It is *produced much more slowly* than in the case of apomorphin, and the *nausea* is in consequence more prolonged. Ipecac increases the *tracheal secretion*, even when given intravenously.

If the drug has been given by the stomach, it is usually

The most important preparations are marked ⁂.

voided by the vomiting, and no further symptoms appear; but if it was administered *hypodermically*, the vomiting is followed by **diarrhea,** which is often bloody.

Central symptoms make their appearance after large doses.

Paralytic symptoms set in, among the earliest in mammals being *vasomotor paralysis* with fall of blood pressure. This is further aided by *weakening of the heart muscle* due to its direct muscle-action, and this results in *death*. If the action has lasted any time, the autopsy will show a marked *gastro-enteritis*, with ecchymoses and even ulcers.

Edema of the lungs, from the hypersecretion of mucus and the weakened heart, is also frequent.

The **local irritation** is one of its important effects. It may give rise to conjunctivitis, bronchitis, pustular eruption on the skin, etc., according to the place to which it has been applied.[1] On hypodermic injection it is very apt to produce local *abscesses*, and more remotely the gastro-enteritis already mentioned. In smaller quantities it produces, especially when given by the mouth, a moderate congestion of the *gastric mucous-membrane*, which may be very desirable in the treatment of some *dyspepsias;* and it also influences the intestinal mucous membrane in a favorable manner in *tropical dysentery*.

Since the desired actions of emetin are the local ones, it is always used in the form of preparations of ipecac, in which its absorption is retarded by the presence of tannin and extractive matter.

IV. MATERIA MEDICA.

Ipecacuanha (U.S.P., B.P.).—The root of *Cephælis Ipecacuanha*, Rubiaceæ. South America; cultivated in India.

Principal constituents: The active alkaloids, emetin and cephælin; tannic acid and a volatile oil, etc.

Simple Preparations:

Extractum Ipecacuanhæ Fluidum (U.S.P., three-fourths alcohol) [*Ext. Ipec. Liquidum*, B.P., alcohol; assayed to contain 2.25% alkaloids]. *Dose:* As expectorant, 0.05 to 0.3 c.c. (1 to 5 minims); as emetic, 2 c.c. (30 minims).

Syrupus Ipecacuanhæ (U.S.P.) (contains Acetic Acid).—7.5%. *Dose:* As expectorant, 0.3 to 1 c.c. (5 minims to 1 drachm).

⁂ *Vinum Ipecacuanhæ* (U.S.P., 10%) [B.P., 5%; assayed to contain 0.1% of alkaloids]. *Dose:* As expectorant, 0.5 to 2 c.c. (10 to 30 minims); as emetic, 15 to 25 c.c. (4 to 6 drachms).

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[1] Some persons are so sensitive to the local action of ipecac that the opening of a jar at a distance of several feet will produce violent sneezing and discomfort.

The most important preparations are marked ⁂.

Acetum Ipecacuanhæ (B.P.).—As the wine.

Trochisci Ipecacuanhæ (U.S.P., ⅓ grain—0.02 Gm.—each) [B.P., ¼ grain—0.015 Gm.—each].

Compound Preparations:

⁂ *Pulvis Ipecacuanhæ et Opii* (U.S.P.) [*Pulvis Ipec. Compos.*, B.P.]. *Dover's Powder.*—10% of each active ingredient. *Dose:* 0.05 to 0.7 Gm. (1 to 10 grs.).

Trochisci Morphinæ et Ipecacuanhæ (U.S.P., B.P.).—Each contains $\frac{1}{40}$ grain (0.0016 Gm.) of morphin sulphate [hydrochlorate, B.P.] and $\frac{1}{12}$ grain [0.005 Gm.] ipecac.

⁂ *Tinctura Ipecacuanhæ et Opii*, U.S.P.—Contains 10% of each. *Dose:* 0.2 to 1.2 c.c. (3 to 20 minims).

(C) THERAPEUTICS OF EMETICS.

I. PHYSIOLOGY OF VOMITING.

The act of vomiting consists in an upward emptying of the stomach, produced by a contraction of its walls and its compression by the abdominal muscles, joined with a simultaneous closure of the pyloric and relaxation of the cardiac sphincters. When the compression of the organ and relaxation of the sphincter do not occur simultaneously, *retching* results, the contents being retained. This frequently precedes the vomiting. A still earlier stage presents the phenomena of nausea as already detailed. The act of vomiting is a reflex one, and to some extent physiologic, especially in young children, where it has little more significance than sneezing. It is controlled by a nerve-center, situated in the proximity of, and closely related to, the respiratory center. The reflex arch might be stimulated at any part of its course, and vomiting thus produced. The *center* may be directly affected by concussion or pressure on the brain, and by drugs which we will call "*general emetics.*"

The *reflexes* may take their origin in many organs: from the alimentary canal—pharynx, stomach, and intestine; from the special senses—by sight, smell, or taste; but in these cases the effect results more strictly from a psychic cause than directly from the sense organs. Disturbance of the mechanism of equilibrium is also an effective cause, as in vertigo and sea-sickness. The impulses may also arise in the gall-duct, kidney, ureter and bladder, sexual organs, etc.

Such irritation may be obtained by any of the known forms of stimulation, and consequently also by drugs, the alimentary canal being the most convenient point for attack. We will call drugs acting in this way *local emetics.* There is still another form of local emetics conceivable, namely,

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The most important preparations are marked ⁂.

those which should *act directly upon the muscular walls* of the stomach without the intervention of the reflex mechanism. But since contraction of the stomach alone does not usually result in vomiting, and since, further, all the drugs which produce this irritation also produce at the same time a reflex irritation, they may well be considered with the last class. We have then, according to their seat of action, two classes of emetics—local and general.

II. ENUMERATION OF EMETICS.

Any irritant substance may act as a *local emetic* when brought in contact with the lining of the alimentary canal and especially of the stomach. The number of irritant substances is very large—they include practically everything; even water in sufficiently large quantity has this effect, especially when warm, and is indeed used as an adjunct to other emetics (its effect being, however, largely mechanical). Besides the substances which have specific irritant properties, those otherwise inert may irritate by their salt action if they are soluble, or by their mere presence if they are not.

Of course, these actions are in very many cases not strong enough to produce even a trace of nausea; nevertheless, the number of substances which may produce emesis, either by their local or general action, affords a very large material, the greater part of which is valueless for practical use, since vomiting forms only one factor in their action. However, it has been possible to select a comparatively small number which show freedom from other actions. It should further be said that very many of the substances which we are now to consider have a central action as well as a local one.[1]

Amongst **local emetics** we have: *1. All salts, and especially the metallic salts.* Especially ZINC and COPPER SULPHATE and **Tartar Emetic** and AMMONIUM CARBONATE.

2. Those acting on muscles or centrifugal nervous mechanism: Nicotin, Morphin, Pilocarpin, *Sanguinaria*, Phytolacca, Lobelin, Muscarin, Physostigmin, etc.

3. Vegetable irritants: **Ipecac**, *Senega*, MUSTARD, *Quillaja*, Digitalis, **Squills**, Quinin, Carbolic Acid, etc.

Of **general emetics,** APOMORPHIN is the main representative.

III. USES OF EMETICS.

Emetics are used for two very different objects: to *produce vomiting or to produce nausea.* The same drug will accomplish both objects, the dose for the latter purpose being about one-tenth of the emetic dose.

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[1] Italics signify that the drug is used mainly as nauseant; small capitals, as emetic; heavy-face type, for both purposes.

The several drugs are especially adapted to one or the other purpose, and it is well to make a selection accordingly.

The indications for the use of emetics were formerly very numerous and general, but they are now obsolete except for very definite objects.

1. **The nauseant stage** is used mainly in the treatment of catarrhal conditions and *coughs*. The *increase of secretions*, especially mucus, is the desired feature in this, and they are only useful when this is deficient or thick and tenacious.

Since the nauseant stage is to be prolonged without reaching actual vomiting, the milder emetics are chosen, and unless there is fever, those having the least depressing action.

The doses given are calculated to be repeated every two hours.

The most important amongst these are:

Emetin (in the form of wine or syrup of ipecac, 15♏ (1 c.c.), or Dover's powder, 2 grs. (0.15 Gm.), the latter also useful on account of its diaphoretic action) (see p. 303).

Saponin (in the form of Syr. Senegæ, ʒss—2 c.c.): This has the advantage of not being absorbed and hence is less depressing.

Ammon. Carbonate (2 grs.—0.15 Gm.): This is actually stimulating and on account of its alkalinity tends to dissolve the mucus.

Tartar Emetic (1 gr.—0.06 Gm.): This is much more depressing, and if long continued may produce symptoms analogous to arsenic. Perhaps the best way of administering it is in the *Comp. Syr. Squills*, 15♏ (1 c.c.).

2. **Actual Emesis.**—(A) The **indications** for an actual emetic action may be summarized as follows:

1. To *remove solid bodies* from esophagus, pharynx, or upper air-passages. (If the obstruction is in the trachea, this is not without danger, since the body may become lodged in the glottis.) *Croupous membranes* may be removed in a similar manner. Similarly, they may cut short an attack of asthma.

2. *To empty the stomach:* (*a*) When the food is not being digested, especially after overeating.

(*b*) *To remove poison:* This is of especial importance in acute poisoning through substances administered by the stomach, but it may even be useful when the poison has been administered in other ways, especially in the case of morphin, when the poison is excreted into the stomach. They are useful in the same way in chronic poisoning, and a beneficial action which has been claimed for them in malaria and other fevers may perhaps be partly explained in this manner. Ipecac is especially useful for the latter purpose, since it also produces diarrhea.

Their use in acute poisoning may often be replaced by the stomach-pump and by lavage. They should be avoided when the poisoning is due to caustics, since the violent compression is apt to cause rupture of the weakened wall of the stomach (this objection is perhaps rather theoretic). In many of these the drug itself causes emesis, so that further measures, except perhaps warm water, are unnecessary.

3. To cause *compression of the liver*, for the removal of bile and small gall-stones from the gall-bladder and ducts: The usefulness of this measure is perhaps doubtful; since the intestines are also compressed, the added vis a tergo can not be very effectual, and on the other hand it might rupture a distended gall-bladder.

(B). The **contraindications** to emetics are mainly due to increase of pressure and to debilitation, and are as follows:

1. Severe *heart-defects*, or *aneurysm* of the aorta, since the sudden and violent increase of intrathoracic and intra-abdominal pressure may result in the rupture of these organs.
2. *Atheroma.* The sudden changes in blood pressure are apt to burst a vessel and produce apoplexy.
3. Similarly, they may lead to hemorrhages in *phthisis.*
4. Abortion may result, in *advanced pregnancy.*
5. Tendency to hernia.
6. In all debilitated conditions there is danger of collapse.
7. Caustic poisoning.

(C) The **measures most commonly adopted to produce emesis** are the following:

1. Warm Water, Tickling of Fauces.—These do not usually act as emetics when the stomach is normal; but when it is irritable—as is usually the case when emetics are indicated—they may be sufficient. But on account of their uncertainty they are usually only employed to aid the action of other emetics.

2. The same may be said of *mustard* (a teaspoonful in a cup of hot water).

These means (1 and 2) do not cause much depression, but they act slowly and are uncertain; they are hence of value for *emptying the stomach* of food, etc., but would *not be indicated in poisoning* where a prompt action is the first requirement. When no other emetic is at hand, they should of course be tried.

3. Salts of Alkalies.—A concentrated solution of any neutral salt may cause vomiting through irritation, but they are uncertain and have no advantage, with the exception of *ammonium salts*. These have a stimulating action on the medulla, tending to counteract the depression; they should be used whenever the latter is especially contraindicated. Their action is too slow and uncertain to be of use in poisoning. Ammonium *carbonate* has the additional advantage of dissolving mucus, and has its special indication in catarrhal conditions. It is given in doses of 10 to 20 grs. (1 Gm.) in solution, repeated until vomiting occurs.

4. Metallic Salts.—Those in practical use are the Sulphate of Copper and of Zinc, and Tartar Emetic. The latter may be to some extent absorbed, and is then very depressing; it is also very slow, so that it may be doubted whether it is ever indicated. Of the former, the preference is given to the copper salt, although the zinc sulphate has precisely the same action. They irritate in a specific manner those structures in the stomach which set up the vomiting reflex, before the protoplasm of the gastric wall has undergone any noticeable change. They are not absorbed so long as the mucous membrane is intact, and are hence quite safe. Their action is rapid, so that there is *no time for nausea*. The depressing action is also small. But they produce practically always some irritation of the gastric walls, and this limits their use to such cases of poisoning in which the poison is not injurious to the stomach itself. They must be especially avoided when there is reason to suppose that the mucous membrane has been injured, since they would be absorbed in this case and cause poisoning. Their only *advantage over apomorphin* consists in a less degree of nausea and depression. Copper sulphate is of especial value in *phosphorus-poisoning* if any of the poison is still in the stomach, since the metallic copper is precipitated and forms an impermeable coating over the unabsorbed phosphorus particles. It is administered in about 1 % solution, 10 grs. (0.7 Gm.) repeated at intervals.

5. Vegetable irritants, including emetin, saponin, digitalin, etc., act slowly and manifest other actions, which practically limit their use to the production of nausea. Ipecac is sometimes used as an emetic (ʒj—4 c.c.—of wine every fifteen minutes).

6. Of *alkaloidal emetics*, not local irritants, *apomorphin* is alone used in practice. It is indicated whenever a prompt emetic is desired. The only exception is formed by cases in which depression is especially contra-indicated; in these, ammonium carbonate should be chosen for slow, copper sulphate for quick, action. Apomorphin is the only emetic which can be given hypodermically, and must therefore be used in all cases where swallowing is impossible. It is used in 1 % solution hypodermically, in doses up to 1/6 grain (0.01 Gm.).

CHAPTER XV.

ACONITE; VERATRIN; COLCHICIN; CARDIAC DEPRESSANTS.

(A) ACONITE GROUP.

I. COMPOSITION, ETC.

Aconite ushers in a series—comprising also veratrin and colchicin—characterized by widespread and confused stimulation and paralysis of nervous structures, both central and peripheral, and, in addition, by a peculiar action on skeletal and cardiac muscle.

Aconite itself is one of the oldest known poisons. The Greeks and Romans were acquainted with its action, and it is altogether probable that when they mention a strong, rapid poison, they used an expressed juice of this plant. The ancient Chinese and Gauls used it as an arrow poison. Its therapeutic use is of much more recent date (it was introduced by Störck in 1762).

The isolation of its toxic principles is quite a recent achievement. Their preparation in pure form is very difficult, as they are easily decomposed into much less active hydration products. Preparations called "aconitin" formerly differed enormously in their strength, some being over a hundred times more active than others, and fatal accidents resulted from their confusion. They are now known to be compounds, after the manner of atropin (see p. 250), between various closely related bases (aconins) and aromatic acids (especially benzoic). The principal ones are:

1. *Aconitin*, from Aconitum Napellus. (It is a benzoic acid-aconin.) The *Japaconitin*, from Ac. Japonicum, formerly supposed to be a distinct alkaloid, is now generally considered identical with aconitin.

2. *Pseudaconitin*, from Ac. Ferox.

3. *Delphinin*, from Delphinium Staphisagria.

The first and second seem to be about equally active; the third is considerably weaker.

The exact chemic structure and composition of these alkaloids are still quite obscure. They agree in giving hydration products which have qualitatively the same action, but are the weaker the more they are hydrated. (Pikraconitin is already only $\frac{1}{50}$ as strong as aconitin; aconin, $\frac{1}{2000}$.)

$$\underset{\text{Aconitin}}{C_{32}H_{43}NO_{12}}\,[1] + H_2O = \underset{\text{Pikraconitin}}{C_{25}H_{39}NO_{11}} + \underset{\text{Benzoic Acid}}{C_7H_6O_2}$$

$$\underset{\text{Pikraconitin}}{C_{25}H_{39}NO_{11}} + H_2O = \underset{\text{Napellin}}{C_{24}H_{37}NO_{10}} + \underset{\text{Methyl Alcohol}}{CH_3OH}$$

$$\underset{\text{Napellin}}{C_{24}H_{37}NO_{10}} + H_2O = \underset{\text{Aconin}}{C_{22}H_{35}NO_9} + \underset{\text{Acetic Acid}}{C_2H_4O_2}$$

Aconitin is the *most toxic of all alkaloids*, and is only surpassed by some of the toxalbumins and similar substances. Three milligrams are fatal to man.

II. SUMMARY OF ACTIONS.

1. Excitation and subsequent paralysis of many different nerve endings—sensory, motor, and secretory.

2. Excitation and subsequent paralysis of certain parts of the central nervous system.

III. DETAILS OF ACTION.

(A) Peripheral.—**1.** The first effect of aconitin—whether on local or systemic administration—consists in a **local irritation** of the *sensory nerves* of the skin and mucous membranes. When applied to the skin in *watery* solution it has very little action, since it cannot be absorbed; but if it is dissolved in *oil*, it causes a pricking, itching, and burning; then, similarly to cocain, a total *paralysis of sensation* to touch, temperature, pain, etc. Applied directly to any kind of nerve-fiber, it destroys its irritability, and the recovery from this is quite slow.

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[1] This formula is not universally accepted, and is given here simply as an instance.

These skin effects also follow its administration by mouth or hypodermically, but in the former case are preceded by similar phenomena in the mouth. There is the same tingling and burning, a *bitter-sour taste*, and disagreeable scratching sensations in the pharynx. Other mucous membranes are also affected and give rise to reflexes (sneezing, coughing, salivation, nausea, vomiting, etc.), which greatly complicate the picture of the intoxication. The irritation is in all cases followed by anesthesia. There is no *reddening* or other sign of inflammation (as there is with most local irritants), even on the mucous membrane.

The great number of structures irritated when the drug acts from the blood would favor the theory that the stimulation is central; but this is disproved by the fact that the action is first seen in the situation where the aconitin is applied.

A peculiar and characteristic effect of aconite, a *chilly sensation* which occurs before either the temperature or the circulation through the skin is changed, must be due to a stimulation of certain temperature nerves, and is of interest since aconitin seems to be the only drug having this action from the blood, although possibly some bacterial poison may also possess it. (Menthol also stimulates these nerves, but only on local application.)

2. The **secretory endings** in general are also stimulated, both directly and reflexly.

Striped muscle shows fibrillar twitchings, which persist after sections of the nerves, but are abolished by curare, and are therefore caused by stimulation of the endings.

3. The effect upon the **heart** is very characteristic and appears somewhat complicated, since all the different parts of the cardiac mechanism are successively stimulated and paralyzed. If we study (**a**) the *isolated* **frog's heart,** we see a series of *phenomena* somewhat as in figure 59:

1. Quickening, from stimulation of the accelerator and automatic mechanism.

2. Accelerator paralysis, beginning stimulation of vagus and beginning paralysis of heart-muscle. These result in slowing, and finally stoppage in 3. In 4 the vagus stimulation is giving place to paralysis, but the paralysis of the cardiac muscle and automatic mechanism has progressed so that the beats are weak and irregular. The automatic mechanism is the next to give out; in consequence the heart stops, but it still responds to direct stimulation. This, too, is finally lost through paralysis of the muscle-fibers.

The peripheral effects upon (**b**) the **mammalian heart** are presumably the same, but are largely obscured by central actions.

The *isolated mammalian heart* (Hedbom-Langendorff) shows the following: The first effects are inconstant; the frequency is then enormously increased and amplitude lessened below what is accounted for by the quickening (increased irritability and weakened muscle). Then follows a transient increase of amplitude (muscular stimulation), and then sudden stoppage of left ventricle (paralysis of automatic property). The right ventricle and the auricles make a few more contractions. Caffein may start a few beats.

(c) **The central action** on the circulation (Fig. 60, *A*) consists in *stimulation, and later paralysis, of the vagus and vaso-motor centers.* The **vagus center** is first affected, even before the peripheral heart-actions appear; hence *small doses* give a pure slowing of pulse with fall of blood pressure. The pulse-wave is dicrotic (Fig. 60, *B*). When the quickening sets in—from stimulation of accelerators, and later from paralysis of the vagus—the tendency will be to a rise of blood pressure, and this will be supported or

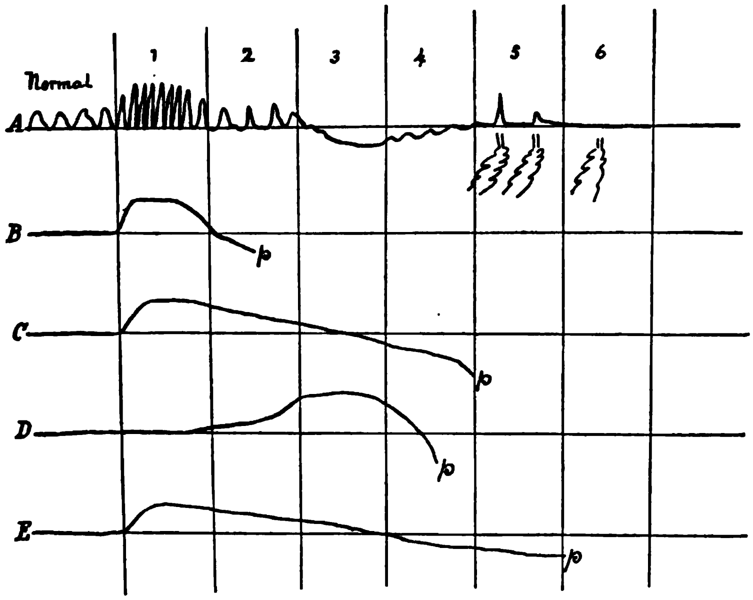

Fig. 59.—Schema of action of aconite on frog's heart: *A* represents diagrammatically the changes noted in the heart; *B* to *E* are to show the part which the different structures of the heart contribute to the observed phenomena; a rise above the base-line is to indicate increased functional activity, and the converse; *p*, point at which paralysis occurs; *A*, normal; *B*, accelerator endings; *C*, automatic property; *D*, vagus endings; *E*, muscle contractility.

counterbalanced by the vasomotor action, according to whether the vasomotor stimulation or paralysis falls in this period. The latter is, however, of less importance. Larger doses act on the heart, and cause it to become arhythmic (Fig. 60, *B*), by increasing its irritability; and later bring it into delirium cordis. The final result in all cases will be a *great fall in pressure* from paralysis of heart and blood-vessels.

(B) Its effects upon the **central nervous system** appear still more complicated if it is attempted to study them in detail; but they become simpler if certain general facts are borne in mind.

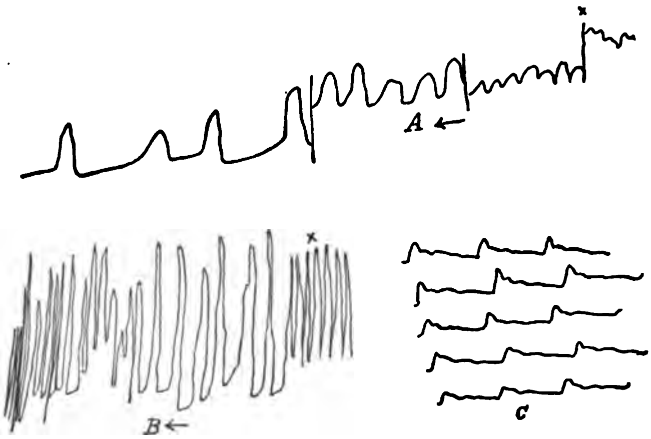

Fig. 60.—Aconite action begins at X: *A*, Carotid pressure, dog; shows progressive vagus stimulation; *B*, cardiomyogram, dog; shows the stages of slowing, irregularity, and final quickening; *C*, sphygmogram, man: the first line is normal; the others show the lowering of the pulse-wave.

The central nervous system is affected through its *whole extent, both directly and reflexly.* The *direct action predominates* and is *mainly paralyzing.* The action is exerted mainly upon the *medulla,* then comes the *cord,* and lastly the *hemispheres.* Consequently the *intelligence* remains unimpaired as a rule, but there may be *unconsciousness* as a consequence of *collapse.* The latter, which occurs early, is the result of *paralysis of the medullary centers.* Of these, the respiration is affected early; it becomes slowed, difficult, and dyspneic. This is partly reflex, from stimulation of the vagus endings in the lungs, etc. Paralysis of the respiratory center forms the *cause of death.* Of *other medullary* structures the vagus and vasomotor centers have been considered.

The *vomiting*, *diarrhea*, etc., may also be due in part to direct stimulation of the centers, but are largely from local irritation.

Convulsions occur; their seat is probably diffuse. The *temperature* falls, both in health and disease, but this is probably an expression of the collapse action.

IV. TOXICOLOGY.

It will be seen from the above that the picture of aconite-poisoning must be a very *complicated* one; the whole nervous system, central and peripheral, being affected, in no well-defined order, in two diametrically opposed directions, the result must be extremely variable, and can be understood only by bearing this diversity in mind.

Accidental poisoning from the fresh plants,—which as monk's-hood or larkspur are quite common in gardens,—as also from liniments, etc., is quite frequent. On account of the small dose, the absence of postmortem signs, and the difficulty of chemic proof, aconitin has recently become quite a favorite for *suicidal* purposes. The use of the plant for *criminal poisoning* is widely spread in the East. The symptoms are so unmistakable—especially the tingling—that it has not found many users in civilized countries.

Symptoms.—In very large doses death may occur almost instantly—probably from paralysis of the heart. In sublethal doses the tingling, slow, weak, and irregular heart, and muscular weakness are most conspicuous. In moderately toxic doses the following picture is seen: *Burning* in mouth, stomach, and skin; excessive salivation; nausea, retching, *vomiting*, and *diarrhea* (both central and reflex effect). The burning passes into anesthesia. There is great restlessness. The *pulse* is slow, feeble, and arhythmic; later it may become very rapid. *Respiration* is dyspneic. There are muscular weakness, incoordination, vertigo. The *skin* is cold and livid. The *pupils* are usually dilated. The *intelligence* does not usually suffer, but there may be stupor and even unconsciousness. The special senses and speech may be impaired. *Convulsions* are common. *Death* may occur by heart paralysis, but more often by paralysis of the respiratory center. The symptoms may appear almost instantly, and are rarely delayed beyond an hour. In fatal poisoning death occurs usually in two to six hours. There are no constant *postmortem changes.*

Treatment.—The usual chemic antidotes. Emetics are not usually necessary. For the rest, the treatment should be mainly stimulating—ammonia, brandy, strychnin, atropin, warmth, and, when necessary, artificial respiration. The *chemic tests* for aconitin are of no value. The poison is best proved by its pharmacologic action on the frog's heart. (This is the more important since, in a legal case, a ptomain was isolated which gave the chemic tests for delphinin. The prickling is also very characteristic. Veratrin is the only other substance having a similar effect.) Aconitin is excreted mainly in the urine.

V. THERAPEUTICS.

The *collapse action* of aconitin is so strong that none of its other effects, except the *local anesthesia,* can be utilized. The former may, however, be useful, especially in short and *sthenic fevers,* as, for instance, in colds; it depresses here the overaction of the heart, and promotes sweating, and in both ways tends to lower the temperature. Very *small doses* should be employed for this purpose—1 drop of the tincture for adults, repeated every hour until the pulse has returned to normal. It should be avoided, just as all other depressing agents, in long-continued fevers, such as typhoid.

Its *anesthetic action* has already been discussed under local anesthetics (p. 238), and it will also be considered under counterirritants (Chap. XXIX, E). It is used in the form of liniments (about 1 part of tincture to 10 of the liniment) and in 2% ointment of the alkaloid, mainly in neuralgias and rheumatism. It is given internally against trigeminal neuralgia.

The staphisagria is used in the form of ointment to destroy pediculi.

VI. MATERIA MEDICA.

Aconitum (U.S.P.) [**Aconiti Radix,** B.P.].—(*Aconite, Monk's-hood, Wolfsbane.*) The tuber of *Aconitum Napellus,* Ranunculaceæ. Europe, Asia, and northwestern North America. (Other species contain similar principles.) Frequently cultivated in gardens. All parts of the plant are poisonous.

Active Constituents: Aconitin and similar alkaloids (in all about 0.07%); resin, fat, sugar.

Preparations (made with ¾ to ½ alcohol; become turbid if mixed with water, but this does not destroy their activity):

Extractum Aconiti.—Dose: 0.006 to 0.015 Gm. ($\frac{1}{10}$ to ¼ grain).

Extractum Aconiti Fluidum.—*Dose:* 0.03 to 0.12 c.c. (½ to 2 minims).

Tinctura Aconiti (U.S.P.).—35%. *Dose:* 0.03 to 0.3 c.c. (½ to 5 minims).

Tinctura Aconiti (B.P.).—5%. Three-fourths alcohol. *Dose:* 0.3 to 1 c.c. (5 to 15 minims).

* **Aconitinum.**—On account of the uncertain strength of the different preparations, this should never be given internally. (Nor has it any great advantage over the tincture for external use.)

The *crystalline* consists of almost pure aconitin, and has the most powerful action (maximal dose: 0.0003 Gm.). The amorphous contains an admixture of the hydration products, and varies accordingly in strength from $\frac{1}{100}$ to as active as the crystalline.

The *aconitin* of the British Pharmacopœia is the amorphous variety. It is employed as a 2% ointment (*Unguentum Aconitinæ*, B.P.).

Staphisagria (U.S.P.) [**Staphisagriæ Semina**, B.P.].—(*Stavesacre, Larkspur.*) The seed of *Delphinium Staphisagria* (other parts of the plant and other species are also poisonous), Ranunculaceæ. Temperate zone.

Constituents: Delphinin and similar alkaloids; fixed oil, mucilage.

Preparation:

Unguentum Staphisagriæ (B.P.).—10%. Used as parasiticide.

(B) VERATRIN GROUP.

I. COMPOSITION, ETC.

This contains a number of alkaloids existing in various species of the genus Veratrum and in some other plants.[1] The principal ones are veratrin (especially in Veratrum viride) and protoveratrin (in Veratrum album).

There are quite a number of other alkaloids present in these plants, but they are not of importance. The commercial veratrin consists of a mixture of veratrin alkaloids. Veratrin and protoveratrin have a chemic composition similar to aconitin.

They agree with aconitin also in their action upon the central nervous system and peripheral endings. But veratrin shows, in addition, a peculiar action in prolonging the relaxation of striped and cardiac muscle.

II. DETAILS OF ACTION.

1. **Striped Muscle.**—When an animal, and especially a frog, has been poisoned with veratrin, it shows very striking peculiarities in its movements. It can contract its muscles with ordinary quickness, but it cannot recover its former position for some little time. The cause of this can be demonstrated on isolated muscle-nerve preparations (Fig. 61.). It will be seen in these that the ascent of the muscle curve is as abrupt as usual, but that the relaxation is enormously

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[1] Commercially it is obtained from the seeds of *Asagræa* (Schœnocaulon) *officinalis* (Sabadilla, Cevadilla), Liliaceæ. Mexico to Venezuela.

* Not official.

prolonged. The muscle remains in what would at first view resemble complete tetanus. This lengthened relaxation goes hand in hand with an increased formation of heat and use of material; it is therefore an active process. It is lessened by fatigue and cold and other agents which depress the muscle (ether), and increased by moderate heat. These facts point to the view that the lengthened relaxation is an expression of greater functional activity. It must be looked upon as a prolonged contracture rather than a loss of elasticity. And this is supported by other actions which the veratrin exerts upon muscle: The tension, the height of contraction, the irritability, and the power of doing work—the lifting and sustaining power—are all increased, and the effects of fatigue are diminished by it.

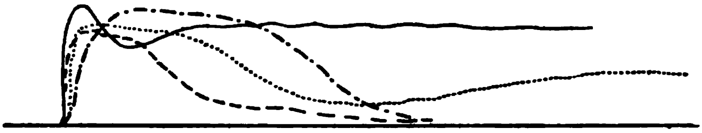

Fig. 61.—Veratrin on frogs' muscle: .... at room temperature (15° C.); ——— at 20° C.; —·—·— at 7° C.; – – – – after fatigue.

These results are best seen on frogs, but may also be noted in mammals. The contraction is not quite smooth, but often shows two to four elevations. This is due to variations in the excitability of the muscle-fiber at different times.

Protoveratrin does not show the above actions, although it temporarily increases the force of the muscular contraction. It seems to exert a special action on *nerve*, prolonging the negative variation. Veratrin does this to a less extent. Both act also in a similar manner on the *nerve endings*. A similar effect is claimed for *smooth muscle*.

2. The **cardiac muscle** is affected in a manner similar to the skeletal. This results in a *quick systole and retarded diastole.* In the frog's heart the auricle is much less affected, so that it may make two or more beats to one by the ventricle. *The isolated mammalian heart* (Hedbom-Langendorff) shows a primary slowing from stimulation of the peripheral vagus mechanism; then irregularity, and finally paralysis of the cardiac muscle, precisely as with digitalis.

3. The **circulation in general** is affected in the same way as with aconitin. *Slowed pulse and lessened blood pressure* are the principal effects, due mainly to its central action. Its *other central actions* (upon respiration, etc.) are practically identical with those of aconitin. (Fig. 62.) In

guinea-pigs it causes a peculiar form of (medullary ?) convulsions, consisting in "bucking" jumps.

4. The **sensory nerve endings** also show the aconitin action, and even more strongly than in the latter. drug. Sneezing and coughing are prominent symptoms. The prickling and smarting are followed by *anesthesia.* Protoveratrin causes the anesthesia without the preceding irritation, and thus resembles cocain.

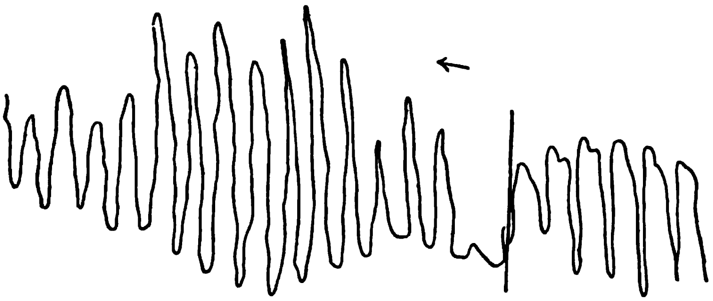

Fig. 62.—Veratrum viride on respiration, rabbit (lever method). Upstroke is inspiration.

5. Veratria produces **vomiting and diarrhea,** for the most part probably reflexly by acting on the sensory nerve endings.

III. TOXICOLOGY.

Poisoning by veratrin is not common. It presents the following **symptoms,** which are also characteristic of aconitin: Burning in mouth, spreading to stomach; increased salivation, vomiting, diarrhea, abdominal pain; anxiety, headache, giddiness; pupils dilated; pulse slow and feeble; weakness, twitchings in muscles. Death by respiratory and circulatory collapse. Consciousness preserved till the end. Postmortem not characteristic.

In *non-fatal doses,* the symptoms are very slow in disappearing, and a double case of *slow poisoning* by continued small doses is on record: The two patients became very weak and thin, suffered from bloody diarrhea, insomnia, disturbance of the intellect, and delirium.

The **treatment** is the same as in aconite-poisoning (see p. 336). As the veratrin is rapidly excreted through the urine, it is well to administer hot tea as a diuretic.

Veratria is easily identified by its chemic reactions (see Chap. XXXIII).

IV. THERAPEUTICS.

It has been used after the manner of aconite, to secure the reduction of temperature by artificial *collapse*. It has no advantages. Its *local irritant* and anesthetic properties have caused it to be used in neuralgia, etc. The oleate is best adapted to this purpose.

V. MATERIA MEDICA.

Veratrum viride (U.S.P.) (American Hellebore).—Rhizome and roots of *Veratrum viride*, Liliaceæ. North America.

Principal Constituents: *Veratrin* (cevadin). Other weak alkaloids: Jervin, pseudojervin, rubijervin, etc. Resin and starch.

Preparations of the U.S.P.:

Extractum Fluidum.—Made with alcohol. *Dose:* 0.05 to 0.3 c.c. (1 to 5 ♏).

Tinctura.—40%. Made with alcohol. *Dose:* 0.1 to 0.5 c.c. (2 to 10 ♏).

Veratrina (U.S.P., B.P.).—A mixture of the alkaloids (usually obtained from plants other than veratrum, especially Asagræa officinalis, U.S.P.). Insoluble in water, soluble in alcohol.

⁂ *Oleate* (U.S.P.).—2% solution in oleic acid.

Unguentum Veratrinæ (U.S.P.).—4%.

Unguentum Veratrinæ (B.P.).—2%.

(C) COLCHICIN.

This substance is of extreme theoretic interest, although it no longer has any practical importance. It exists, along with another similar alkaloid, colchicein, in Colchicum autumnale. It differs in certain characters from ordinary alkaloids, but its constitution is almost unknown.

Its action on mammals does not appear for a considerable time, even after intravenous injection, and it has almost no action on frogs. The reason for this is, that it is not the colchicin itself which produces the symptoms, but an oxidation product—oxy-di-colchicin—which is formed from it in the mammalian organism,—even by circulating it through excised organs,—but does not seem to be capable of formation in the frog's. Once formed, whether in the above manner or artificially by the action of ozone, it is toxic to frogs also.

The actions on the *sensory endings* and on the *heart* are similar to those of aconite and veratrin; the action on the *central nervous system* is almost purely depressant. This is in part secondary to the effect upon the *abdominal organs*. Colchicum causes extremely violent and quite uncontrollable vomiting and diarrhea. This is not an inflammatory action, for the intestine may appear quite normal after death. If

The most important preparations are marked ⁂.

ecchymoses, etc., are present, these are to be ascribed to the mechanical effects of the extremely violent peristalsis. The cause appears to be an increased irritability of the intestinal tract, so that the normal impulses, which ordinarily keep up a moderate peristalsis, now produce an extremely violent one. No further explanation can be offered at present.

TOXICOLOGY.

The **symptoms** of colchicum-poisoning do not appear for some time. Once they set in, they cannot be controlled; colchicum is therefore one of the most fatal of poisons. The symptoms refer primarily to the digestive tract: burning pains in abdomen, extremely violent vomiting and diarrhea, stools often bloody. For the rest, they are those of collapse, consciousness not being affected. *Death* occurs by failure of respiration. The *postmortem* appearances are not characteristic. There may, as has been said, be appearances of injury to the intestines from the strong peristalsis.

The **treatment** of poisoning, besides the usual alkaloidal antidotes, must be symptomatic.

THERAPEUTICS.

It will be seen that the pharmacologic actions of colchicum furnish no guide to its rational therapeutic application. It has been widely used on empirical grounds against *gout and rheumatism.* There is but little evidence of any superiority over aconite, and its uncertain toxicity renders it so dangerous that its use should be unhesitatingly condemned. (However, authorities disagree very much on this point.)

MATERIA MEDICA.

Colchici Radix (U.S.P.) [**Colchici Cormus**, B.P.].—The bulb of *Colchicum autumnale* (Meadow Saffron), Liliaceæ. Europe.

Colchici Semina (U.S.P., B.P.).—The seed of the above.

Principal Constituents.—Root: Colchicin, 0.5% ; Starch, Gum, Resin, Fat, etc. Seed: Colchicin, 0.3%, etc.

The colchicin is contained in all parts of the plant.

Preparations from the Root:

Extractum Colchici Radicis (U.S.P.).—Made with acetic acid. *Dose:* 0.03 to 0.1 Gm. (½ to 2 grs.).

Extractum Colchici Radicis (B.P.).—Made from the fresh corm. *Dose:* as above.

Extractum Colchici Radicis Fluidum (U.S.P.).—Two-thirds alcohol. *Dose:* 0.1 to 0.5 c.c. (2 to 8 minims).

⁂ *Vinum Colchici Radicis* (U.S.P., 40%).—*Dose:* 0.3 to 1 c.c. (5 to 15 minims). [B.P., 20%. *Dose:* 0.3 to 2 c.c. (5 to 30 minims)].

The most important preparations are marked ⁂.

Preparations from the Seed:

Extractum Colchici Seminis Fluidum (U.S.P.).—Two-thirds alcohol. *Dose:* 0.05 to 0.3 c.c. (1 to 5 minims).

Tinctura Colchici Seminum (U.S.P., 15%) [B.P., 20%].—One-half alcohol. *Dose:* 0.5 to 2 c.c. (10 to 30 minims).

Vinum Colchici Seminis (U.S.P.).—15%. *Dose:* as the tincture.

(D) CARDIAC DEPRESSANTS.

Cardiac depressants may be defined as drugs which lower the activity of the heart. They may do so either by weakening the cardiac muscle or by stimulating the vagus mechanism. The former is done by large doses of almost any drug; the latter is alone useful therapeutically. A slowing of this kind may be useful in regulating an overstimulated heart; but since it also produces a fall of blood pressure, it is particularly useful when a quick pulse is joined with a high pressure—as in sthenic fever. Quick pulse with low pressure indicates digitalis or strychnin, which act on the vasomotors as well.

The most useful Cardiac Depressants are: Aconite, Sparteïn, Veratrin, Colchicin.

CHAPTER XVI.

QUININ GROUP.

This group contains certain of the cinchona alkaloids, especially quinin. The others, amongst which cinchonin and cinchonidin are the most important, are rather more convulsant; but they have not so far been sufficiently studied.

This group differs from those preceding in having a very marked *toxic action upon unspecialized protoplasm*, an action which exists to some extent in probably most of the alkaloids, but is generally obscured by their selective action on muscle and nerve. The phenomena which are noted with quinin are those of slowly dying tissues generally; an increased functional activity, followed by a diminution or cessation of function. On the whole, the paralyzing action is with quinin the most conspicuous and the most important.

Large doses may produce paralysis directly, without preceding stimulation.

I. SUMMARY OF ACTIONS.

1. A toxic action upon all protoplasm, and an inhibition of ferment action.
2. A specific toxicity to the malaria organisms.
3. A diminution of heat-production in fever by direct action on the heat-producing foci.
4. A depressing action on the central nervous system, preceded by an obscure stimulation.

II. DETAILS OF ACTIONS.

1. General Toxicity.—The toxic action on protoplasm may be seen on lower organisms and isolated cells of all kinds. It acts most strongly on *cells possessed of ameboid and similar movement;* on infusoria, white blood-cells, ciliated epithelium, spermatozoa, insectivorous plants, muscle, etc.

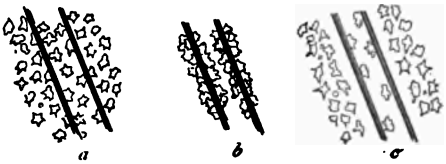

Fig. 63.—Diagram to illustrate the action of quinin on leucocytes, modified from Binz ("Das Wesen der Chininwirkung," Berlin, 1868). The thick lines represent the walls of the blood vessel, and numerous leucocytes are shown both inside of it and outside, distributed through the adjoining tissues. *a* represents the vessel before, and *b* after, the *local* application of quinin. The leucocytes outside the vessel have their movements arrested, and cannot wander on through the tissues, while those inside are not affected and continue to emigrate; *c* represents the effect of quinin injected into the circulation or lymph-sac. The leucocytes inside the vessel are here affected first and their emigration stopped, while those outside still continue to travel onward.

A solution of 0.5 to 1 in 1000 is sufficient to inhibit the movements of *leucocytes* on the warmed slide, and a somewhat larger dose causes their disintegration. It acts in this manner also in the intact organism in the frog (Fig. 63). When the mesentery of this animal is exposed, leucocytes in active motion are seen inside and outside of the vessel (Fig. 63, *a*). If quinin is now applied, the movement of the cells outside of the blood will be arrested, whilst those in the blood stream still emigrate. The result is an accumulation of cells about the vessel wall (Fig. 63, *b*). If the quinin is injected into the vessel, the reverse takes place. The movement of the cells in the blood is arrested, preventing emigration, whilst those outside do not come into contact with the poison, continue to move away, and leave a clear zone about the vessel (*c*). This action does not come into play in mammals, since the necessary dose would kill the animal. It is stated, however, that quinin diminishes the number of leucocytes in the blood.

2. A much weaker, but none the less certain, action is seen on **yeast and bacteria.** The solution must contain 2 to 8 in 1000.

3. **Striped Muscle.**—The strength of the individual contractions may be increased as much as six times by moderate doses, but the muscle is much more quickly fatigued, so that the total work is less than in the unpoisoned muscle. As the same phenomenon is observed in curarized muscle, it must depend upon a direct action on the muscle-fibers. Somewhat stronger doses lower the contraction from the start (Fig. 64). Strong solutions produce a rigor after the manner of caffein.

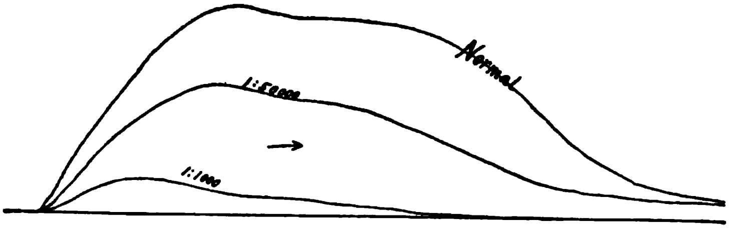

Fig. 64.—Quinin on muscular contraction.

4. The **cardiac muscle** in the frog is slowed by 1 : 50,000 solution and weakened in its contraction; its effectiveness is consequently diminished. The slowing occurs after atropin, and is therefore muscular. A 1 : 5000 solution kills the heart in a few minutes.

5. **Mammalian Circulation.**—In mammals and man small doses cause first a *quickened pulse* with *rise of blood pressure.*

The cause of the former is still under dispute, but is perhaps central. The rise of pressure depends mainly upon a *vasoconstriction,* but the cause of this is also still undetermined. It may possibly be due to a direct stimulation of the unstriped muscles of the blood-vessels.

Larger doses (in man, from 1 Gm. upward) cause a fall of blood pressure and slowing and weakening of the heart from the outset.

The fall is due in part to *vasodilatation.* The slowing and weakening of the heart are analogous to those observed in the frog. It is seen in the *excised* organ (Langendorff method). In this it often causes irregularity, but may regulate the heart if it is already irregular.

6. **Smooth Muscle.**—This shows no marked reaction to quinin.

But this is not saying that quinin does not act upon it, for a slight action on smooth muscle is *not easily accessible to observation*. It is certainly not very strong; the most likely example would be its action on the arterioles. *Contractions of the spleen, uterus, and intestines*, which may sometimes be seen, have been referred to such a direct action on smooth muscle, but this explanation is not very probable, since these phenomena are observed in only a very small percentage of cases; and as these contractions are never followed by paralysis, this would be opposed to all the other actions of the drug. No explanation can be given.

7. Another manifestation of the toxic action of quinin is in **the local irritation** which it produces at the place where it is applied. When given hypodermically it gives rise to severe pain, and may lead to *abscess formation*. When given by the stomach it causes in large doses *gastralgia, nausea*, vomiting, and diarrhea. It also retards the *absorption* of salts, and probably of food. Its excretion through the kidneys may give rise to *albuminuria and hemoglobinuria*. And it seems not unlikely that a *skin eruption* which is sometimes observed, results from the irritant effects of its excretion through this channel.

8. The action of **unformed ferments** is retarded by it. Evidences of this antiferment action may be seen in many directions. The most important are: Diminution of the *oxygenating power of blood* and of protoplasm; slowed acidification of shed blood; lessening of the amount of hippuric acid formed when benzoic acid is circulated through the excised kidney. Of the digestive ferments, pepsin and trypsin are hindered, ptyalin and diastase less so. It also lessens the glycogenetic function of the liver; *i. e.*, the postmortem transformation of the glycogen into sugar.

9. **Effects upon Digestion.**—These can easily be deduced from the above data: It hinders the action of the ferments and absorption of the products. A favorable action which it might be supposed to possess as a bitter is largely counterbalanced by the unfavorable actions mentioned; consequently the utilization of food tends to be lessened when even small doses are used continuously.

10. **Effects upon Metabolism.**—An influence upon this belongs to the earliest actions, and may be obtained even with doses too small to show any other effect.

From its toxic action on protoplasm one would expect to find first an increase and then a lasting diminution of metabolism, corresponding to the increase and diminution in functional activity.

This is indeed what is seen in regard to the excretion of *nitrogen*. There is first a slight increase, then a very marked diminution, which may reach as much as 39% with large doses.

One would be tempted to ascribe this diminution of nitrogen to the diminished utilization of food. Although this undoubtedly plays a part in it, the diminished excretion is out of all proportion, so that the nitrogen content of the body increases. Large doses of cinchonidin have a similar action.

This marked influence upon nitrogen metabolism is in conspicuous contrast to its want of influence upon *oxidation*. The quantity of O absorbed and CO_2 given off is practically unaffected by medicinal doses (up to 1.5 Gm.). There is a slight increase, but not more than can be accounted for by the excitement, chilliness, etc.

These effects upon metabolism are of great importance in explaining the effects upon temperature, as will be seen. But before taking up this subject, it is necessary to study the effects upon the central nervous system.

II. The effects upon the **central nervous system** consist in a rather *slow general paralysis*, probably preceded by stimulation; the latter is rather difficult to make out in mammals. In *frogs* there is first an increased reflex irritability. This is followed by loss of spontaneous movement, then paralysis of respiration, and lastly of the cord, the phenomena bearing a general resemblance to those of the action of morphin (see p. 198).

The stage of stimulation is said to be more marked with cinchonin and cinchonidin, since these produce convulsions.[1] These are epileptiform in character, but their seat has not yet been definitely located. Probably they are not confined to any one center. In other respects these alkaloids agree qualitatively with quinin.

The depressing effects upon the hemispheres are much less marked in *mammals*, but a *diminished appreciation of pain* can be distinctly made out, and upon it rests the employment of quinin against neuralgic and rheumatic pains.

One of the most constant early symptoms of larger doses of quinin is headache, ringing in the ears, and disturbed vision, a complex of symptoms grouped together under the name of *cinchonism*. These are not due to any action on the central nervous system, but to *local changes in the circulation*.

In the case of the *ear* there is a marked *hyperemia*, which can be made out by direct examination. It may lead to chronic inflammation. The *retina*, on the other hand, shows a *constriction* of its vessels. No explanation has yet been offered for these local vascular changes. They are to a great extent subject to *idiosyncrasy*, being much more pronounced in some individuals than in others.

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[1] The samples (Schuchardt's) examined by the author had, however, very little convulsant action; the cinchonin had more than the cinchonidin.

The constriction of retinal vessels may be so severe with large doses as to cause degeneration of the ganglion cells from insufficient nutrition. It may also lead to exudation into the retina, and hence permanent blindness. For this reason, nitrites have been suggested as treatment, before the exudation has formed.

With still *larger doses*, there are *photophobia*, *deafness*, and *blindness*, at first partial, later complete. These are probably partly central. There are *difficulty of speech*, *confusion of ideas*, *somnolence*. Then *loss of consciousness*, alternating with *delirium*, *coma*, and at times *convulsions*.

It has been doubted whether the latter are really due to quinin or to the accidental presence of some of the convulsant cinchona alkaloids.

General paresis may appear, preceded by general depression and muscular weakness. The final symptoms are those of *collapse*, due to general paralysis of the central nervous system, and in part also of the heart. The *respiratory center* shows a short primary stimulation with following more marked paralysis. The latter is the usual *cause of death*. But since the medullary centers are not markedly affected until very late, quite large doses are often survived. The *fatal dose* is usually given as 8 Gm., but 30 Gm. have been recovered from.

It is doubtful, however, how much of this really entered the circulation, since the sulphate is very insoluble, so that a large amount may not have been absorbed.

The *peripheral nerves* are not markedly affected, except the poison be applied directly, when it will, of course, kill them just as other protoplasm.

12. Effects on Temperature.—*When the temperature is normal*, small doses of quinin cause a slight rise. In somewhat larger doses, but not sufficient to cause a marked collapse, it gives an insignificant fall. In doses which produce collapse it causes, of course, a marked fall of temperature through this condition—*i. e.*, by lowering the circulation and the respiratory exchange.

In hyperpyrexia the temperature is markedly lowered even by moderate doses.

This antipyretic action is not as pronounced as with the antipyrin and salicylic acid groups.

The *cause of this reduction* of febrile temperature appears to be quite complicated, but it consists mainly in a *diminished heat production through a direct action on the heat-producing foci.* It could conceivably result from one or more of the following:

Diminished Heat Production:	**Increased Heat Loss:**
Direct action on heat-producing foci.	Direct action on vasodilator mechanism of skin.

Indirect action on heat production and dissipation through thermo-regulating centers.

General collapse action.

Calorimetric experiments show that the heat production is considerably diminished, whilst the heat loss is not greatly increased. Consequently quinin acts mainly upon *heat production.*

Quinin produces a slight *dilatation of the cutaneous* vessels, which, since the general blood pressure is not diminished by ordinary doses, increases the heat loss. But since this occurs also with normal animals whose temperature is not markedly affected by quinin, it cannot play a very important rôle.

Quinin lowers the temperature in animals in which the *spinal cord* has been divided. Consequently, its action is mainly *peripheral,* although any collapse which it may produce would also express itself in a fall of temperature.

The evidence so far, then, indicates that *the action is a local one upon the heat-producing foci;* and this is indeed what one would have expected *a priori.*

The most important seat of heat production is in the muscles; next, in the glands. We have already seen that quinin at first increases and then diminishes muscular work, and it is not unreasonable to suppose that it would have the same effect upon the production of heat in these organs. And it will be remembered that the heat production of the body is, in accordance with this explanation, at first increased, then diminished by it. There is less direct evidence in regard to its action on glands and other body-cells; but when the general depressing effect upon all cells is remembered, and, further, its interference with ferment actions, inside and outside of the cell-body—actions which play so large a part in metabolic processes—it seems very reasonable that the general metabolism, and in consequence the production of heat, should be lessened by it in cells other than those of the muscle.

We find a direct evidence of its effects upon metabolism in the excretion of nitrogen, since this is at first slightly increased, but later largely diminished. But here a difficulty arises. We have been accustomed to look upon the excretion of CO_2 as an index of chemic changes resulting in the liberation of energy and consequently of heat; and the excretion of CO_2 is not affected by quinin. But since the calorimeter shows conclusively that the production of heat *is* diminished by it in fever, this interesting fact merely forces us to the conclusion that oxidation is *not* the only source of heat; that heat may also be liberated by other changes—by the splitting or hydration of nitrogenous molecules, in the course of which the nitrogen is converted into urea; and that these changes are those which are hindered by quinin. If it be supposed that this form of heat production is especially prominent in fever,—and this seems quite probable,—the fact that quinin acts on febrile, and not on normal, temperature is also explained.

13. Action on Malaria.—The specific action of quinin in this disease is due to its toxic effects upon the protameba causing the disorder.

This is especially susceptible to it. On a slide a 1 : 10,000 solution immediately arrests the movements of the parasite, and similar phenomena occur in the body. About three hours after the administration of quinin by the mouth, the endoglobular forms of tertian and quartan fever become immobile, granular, lose their nucleoli and their affinity for certain stains. Several hours later they may be seen deformed and fragmented.

The quinin does not act equally on the parasite in all the stages of its development. Its strongest action is upon the forms which are just breaking into spores (Fig. 65, 10), and upon the free-swimming organisms (11); it is much weaker upon the older segmenting bodies (7 to 9), and least upon the young endoglobular forms (1 to 6).

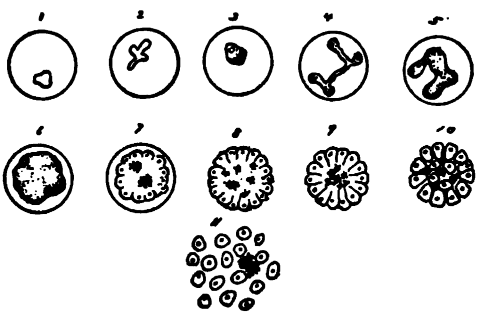

Fig. 65.—Some of the principal forms assumed by the plasmodium of tertian fever in the course of its cycle of development (after Thayer and Hewetson).

Since the latter exist in the blood just before the paroxysm, and their sporulation gives rise to the characteristic chill and fever, and since quinin does not act upon them, it will not be effectual against the oncoming paroxysm. But if it is given at this time it will be present in the blood when the spores are liberated, and as these are most susceptible to its action, it will kill them and thus prevent the development of the new cycle (providing that the dose has been sufficiently large). It should therefore be given several hours before the expected paroxysm, so as to allow time for its absorption. The dose should then be quite large: 1 to 2 Gm. given two to three hours before the expected attack (which will in all probability occur), or 0.3 Gm. four to five times a day in the interval. It also seems to act as a prophylactic. It must be taken continuously for this purpose, since it is quite rapidly excreted—0.1 to 0.2 Gm. every morning.

III. OTHER THERAPEUTIC USES OF QUININ.

1. **Fevers.**—The antipyretic effect of quinin may be used in any fever; but the coal-tar antipyretics have largely forced quinin out of this field. It possesses an advantage over these in a more prolonged action and in less risk of collapse; but it does not take effect as rapidly, and the large doses required—0.3 to 1 Gm.—produce the annoying cinchonism. This can be greatly lessened by giving it with a bromid. Another unpleasant side-action seen in a few individuals consists in a *scarlatinal dermatitis or urticaria.* It is said that this is abolished by atropin. Like the other antipyretics, it is most efficient when the temperature has a natural tendency to fall. It takes about two hours to act, and should, therefore, be given about that time before an expected fall of temperature.

It has been suggested that its efficiency in fever is due to an antiseptic action on the blood. This is not the case, since bacteria are very resistant to it, and would not be affected by it in the concentration in which it could exist in the blood.

2. **Splenic Enlargement.**—In the spleen of malaria its effect is, of course, largely secondary; but good results have been claimed for it in other cases. If this be true, they could perhaps be connected with its action in diminishing the number of leucocytes.

3. **Neuralgias and headaches** are sometimes benefited by its use. The cause of this action is still obscure. It may be due to its general analgesic action. Another theory which has been suggested is, that these neuralgias, etc., are due to the presence of nitrogenous waste-products, and that quinin acts by limiting the formation of these.

4. **Colds** are frequently treated by it, in doses of from 0.06 to 0.2 Gm. (1 to 3 grs.). When it has any effect at all, this must depend upon its anodyne and antipyretic actions.

5. **As a bitter** substance it may act as a stomachic and consequently as a tonic; but it is rather inferior to other bitters, since its continued use leads to an impairment of digestion and of absorption.

IV. METHODS OF ADMINISTRATION.

The administration presents some little difficulty, since on the one hand certain of its salts are very little soluble, and the others have a very bitter taste.

Small doses of quinin sulphate or hydrochlorate may be easily given in the forms of pills or capsules; or in solution, the taste being disguised by glycyrrhiza. (No acid must be prescribed with the latter!) The tannate or the pure alkaloid may also be given, but they are probably less efficient. Being insoluble, they are practically tasteless, and act only as they enter into combination with the acid of the gastric juice.

Large doses of quinin sulphate in pills or powder are probably largely wasted, since they are not dissolved or absorbed; the sulphate requires 740 parts of water for solution. The hydrochlorate is more soluble (1 : 35), but the bisulphate is the best (1 : 10).

It is customary not to prescribe the bisulphate directly, but the sulphate brought into solution by the addition of a sufficient quantity of dilute sulphuric acid. The quantity of acid should be rather in excess. If it is only just sufficient, some sulphate will be precipitated on the tongue by the alkaline saliva, and give rise to a very persistent after taste. There will be very little of this if an excess of acid is used and the mouth rinsed afterward.

The *hypodermic use* of quinin is very painful and gives rise to considerable irritation. It is only justified when a very prompt action is required. It is then injected deeply into the tissue of the gluteal muscle.

The best method is to combine it with antipyrin (three parts of the quinin hydrochlorate to two of the antipyrin), since this greatly increases the solubility.

It has also been used in intravenous injection, but this would require great caution on account of its action on the heart.

Quinin is fairly readily *absorbed* from the stomach and *excreted* in large part unchanged in the urine, most of it very quickly. Other excretions may also contain it.

V. MATERIA MEDICA.

Cinchona (U.S.P., B.P.).—*Peruvian Bark.*—The bark of various species of *Cinchona* (Rubiaceæ). They must contain at least 5% of total alkaloids, and at least 2.5% of quinin.

Cinchona Rubra (U.S.P., B.P.).—The bark of *C. succirubra.*

The trees yielding cinchona are indigenous to the mountainous districts of the Andes in South America. The natives were acquainted with the medicinal value of this "tree of health," and the bark was brought to Europe by the early explorers. It received its name, cinchona, from the Countess Chinchon, who was one of the first to receive its benefits.

At present practically all the barks of commerce are from cultivated trees. This cinchona cultivation is carried on in a number of subtropical mountainous countries possessing a rather moist climate—especially in India.

The U. S. Pharmacopœia does not discriminate between the different species. Between thirty and thirty-six of these are recognized; but many are probably mere variations and hybrids. The most important are: C. Calisaya (yellow bark); succirubra (red bark); officinalis; lancifolia; micrantha; scrobiculata.

The *constituents* are: Certain acids (quinic, quinovic, etc.); *Tannin*, as cinchotannic acid (2 to 4%), which yields green color with iron; cinchona red, a derivative of the preceding; gum, wax, resin, etc.

A very large number of alkaloids have been isolated; many of these undoubtedly arise in the course of the manipulations. The most important are in italics:

Quinin,[1] *Quinidin*, Quinicin.
Quinamin, Conquinamin, Quinamidin, Quinamicin.
Cinchonin, *Cinchonidin*, Cinchonicin, Homocinchonicin.
(Those on a line are isomeric.)

When the crystallizable alkaloids have been separated from cinchona extracts, evaporation of the mother liquor yields a brown extract, *Chinoidin* (Quinoidin), which contains amorphous alkaloids, mainly Di-cinchonicin and Di-quinidin.

**Cuprea Bark*, from Remija pedunculata, Rubiaceæ, contains for the most part the same alkaloids, but no cinchonidin. It is used in the manufacture of quinin.

Preparations.—These have no advantage over quinin, and since they are incompatible with iron, and the alcoholic preparations also with water, the alkaloid should be preferred.

Infusum Cinchonæ (U.S.P.).—6% with 1% aromatic sulphuric acid. *Dose:* 30 to 60 c.c. (1 to 2 ozs.).

Infusum Cinchonæ Acidum (B.P.).—5%. Contains a small proportion of aromatic sulphuric acid. *Dose:* As the infusion.

Extractum Cinchonæ (U.S.P.).—*Dose:* 0.3 to 2 Gm. (5 to 30 grs.).

Extractum Cinchonæ Fluidum (U.S.P., B.P.).—*Dose:* 0.5 to 4 c.c. (10 to 60 minims).

Tinctura Cinchonæ (U.S.P., B.P.).—20%. *Dose:* 2 to 8 c.c. (½ to 2 drachms).

⁂ *Tinctura Cinchonæ Composita* (U.S.P., B.P.).—10% of Red Cinchona; Bitter Orange, Serpentaria.

The above preparations contain glycerin and 66 to 80% of alcohol.

**Tinctura Cinchonæ Detannata*, N.F.—The official tincture with the tannin removed by iron.

⁂ *Elixir Cinchonæ* and *Elixir Cinchonæ Detannatum*, N.F., contain 3% of Cinchona. *Dose:* ad libitum.

**Elixir Quininæ Compositum* (a substitute for cinchona). 0.2 quinin sulphate, 0.1 cinchonidin s.; 0.1 cinchonin s.; in 100 c.c. Aromatic Elixir.

Alkaloids and their Salts.—Their *dose* is 0.03 to 1.5 Gm. (½ to 25 grs.) [0.03 to 0.05 as tonic; 0.05 to 0.25 for colds; 1.0 in malaria].

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[1] Name from *quina*, bark.

* Unofficial.

The most important preparations are marked ⁂.

One part of salt is soluble in:

	SOLUBILITY.	
	Water, Parts.	Alcohol, Parts.
Quinina	1670	6
⁂ *Quininæ Sulphas*	740	65
Quininæ Bisulphas	10	32
Quininæ Hydrobromas	54	0.6
⁂ *Quininæ Hydrochloras*	34	3
Quinidinæ Sulphas	100	8
Cinchonina	3760	116
Cinchoninæ Sulphas	66	10
Cinchonidinæ Sulphas	70	66

* ***Chinoidin.*** Same dose.

Preparations.

The N.F. *Elixirs:*

*Elixir Quininæ Compositum; Elixir Quininæ et Phosphatum Compositum; El. Cinchonæ et Ferri; El. Cinch., Ferri, Bismuth, et Strych.; El. Cinch., Ferri, et Bismuth; El. Cinch., Ferri, et Calcii Lactophosphatis; El. Cinch., Ferri, et Pepsini; El. Cinchonæ, Ferri, et Strychn.; El. Cinchonæ, Pepsini, et Strychn. *All contain 0.4% of cinchona alkaloids.* (Teaspoonful = 0.016.) *Dose:* 4 to 8 c.c.

Syrupus Ferri, Quininæ, et Strychninæ Phosphatum. — Quinin Sulph., 3%; Strychnin, 0.02%; Ferric Phosphate, 2%.

A favorite way of giving quinin for malaria in India is in the form of *Warburg's Tincture*—* *Tinctura Antiperiodica,* N.F. This contains 2% of Quinin Sulphate (each tablespoonful = 0.3 Gm.) and carminatives (rhubarb, aloes, camphor, and aromatic drugs) which probably aid in the absorption of the quinin.

Warburg's Pills.—**Pilulæ Antiperiodicæ,* N.F., contain the same ingredients in solid form. (The pill form is quite irrational.) Each pill = 4 c.c. of the tincture.

* Not official.
The most important preparations are marked ⁂.

CHAPTER XVII.

SERIES OF COAL-TAR DERIVATIVES.

THE former high price of quinin caused chemists and pharmacologists to look about for cheaper efficient substitutes. It was attempted to make quinin or similar substances synthetically, departing from quinolin, one of the decomposition products of quinin. Whilst this search did not result in an artificial quinin, nor even of any substance analogous to it in action, it brought to light a very large number of substances, in some respects even more valuable than the alkaloid itself, and served to direct attention to the pharmacologic significance of the derivatives of the aromatic series, or, as they are more commonly called, of coal-tar.

These possess a number of actions in common, principal amongst these being—

Summary of Common Actions of Coal-tar Derivatives:

1. On the central nervous system, stimulation followed by paralysis, the latter predominating.
2. An antipyretic action on the heat-centers.
3. An irritant and toxic action on protoplasm.
4. A quinin action on muscle.
5. The formation of methemoglobin.

The actions are exerted in a different manner and to a different degree by the several members of the series, mainly in two directions, so that two groups can be made out.

(*A*) *Antipyretic Group.*—This is distinguished by the predominance of the action on the heat-regulating center.

(*B*) *Antiseptic group*, characterized by a much more marked local action on protoplasm, which determines the usefulness of the members as antiseptics. The effect upon the thermic center passes much more readily into general collapse than with the former group.

Relation to Quinin.—It will be seen that the action of the series agrees in a general manner with that of quinin, the principal difference lying in the degree in which the different actions are exerted. In the antipyretic group the principal effect is upon the heat-regulating center, and in the antiseptic group upon the protoplasm, and so violent that it produces necrosis locally and collapse centrally. Quinin has both these actions in a less pronounced degree, producing its main effects by a mild paralyzing action on protoplasm. On the other hand, none of the coal-tar products possesses the specific anti-malarial power of quinin.

(A) ANTIPYRETIC GROUP.

This comprises a very large number of compounds; the most important, however, can be arranged under four headings:[1]

1. *Acetanilid* (antifebrin), with the similar compounds exalgin and benzanilid.

2. *Phenacetin*, with lactophenin and salophen, and its compounds phenocoll and salophen.

3. *Antipyrin*, and some of its compounds, resopyrin (with resorcin), hypnal (with chloral). Antipyrin is derived from phenylhydrazin, and some other derivatives of this substance are also employed: pyrodin (with acetic acid), antithermin (with lactic acid), etc.

4. *Kairin* and *Thallin*, which are quinolin derivatives.

I. DETAILS OF ACTIONS.

1. Action on Temperature.—The effect upon the *normal temperature* is slight, just as in the case of quinin, and may result in a small rise, unless with doses sufficiently large to produce a marked collapse action; but *febrile temperature* is in most cases reduced to normal, or even below, by even moderate doses. What is the cause of this heat-regulating action?

The reduction of temperature is accomplished mainly by an *increased heat loss*. This can be shown by *calorimetric experiments* upon rabbits in which hyperpyrexia has been established by *puncture of the corpus striatum*. The action is central, for it does not occur after section of the cord. An increased heat loss, again, may take place through an increased production of sweat, or by exposing a larger amount of blood to the cooling influence of the surroundings by *dilatation of the cutaneous vessels*. In the case of this group it is accomplished mainly by the latter means.

The dilatation can be plainly shown by the plethysmograph. And since the reduction occurs even after atropin, which suppresses the secretion of sweat, the latter is not essential. The *vasodilatation is confined to the cutaneous vessels*, and this is important, since, if the blood-vessels in the remainder of the body were also dilated, the circulation through the skin would be diminished rather than increased. This limitation of the vasodilatation to the region concerned with the regulation of temperature also points to the central action.

There is also some diminution of the heat production by limitation of the *metabolism*. When the temperature of an animal is *normal*, the members of this group have no very constant or marked effect upon nitrogenous metabolism; perhaps generally at first a small increase, followed by a diminution. Antipyrin, in doses of 2 to 3 Gm., causes a small but unmistakable decrease in both gaseous exchange and nitrogen excretion. In *fever*, however, the diminution in metabolism is quite marked, but comes on *after* the fall in temperature has set in, and must be regarded as an effect, and not a cause, of this fall. The metabolism is always abnormally high in hyperpyrexia, and removal of the latter brings with it a decrease in the former.

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[1] For the composition of these see p. 364.

Antipyrin and the other drugs of this group act, then, upon the heat-regulating center when the temperature is abnormally high, and cause its reduction to or near normal, by increasing the heat loss.

This action must be conceived as a restoration of the centers to their normal pitch. Numerous facts go to show that in fever, as well as in health, the center exerts a regulating influence; but the temperature which it strives to maintain is an abnormal one. Whether this fixation of the temperature regulation at the normal limit is a stimulating or a depressing action of the antipyrin is still under discussion.

The structure of the heat-regulating centers must be conceived as very complicated. There must be neurons regulating the heat production and the heat loss, and it is not inconceivable that there may be separate sets for raising and for lowering these functions. The action of drugs is not usually so sharply specialized that one would expect *a priori* that it would be possible to act upon one of these without, to some extent, involving some of the other closely related structures—both in the way of stimulation and of paralysis. The final result will be the algebraic sum of these actions.

The result will also depend to a very great extent on the previous functional activity of the centers. Thus, there is a peculiar difference in the susceptibility of *different fevers* to antipyretic drugs: High continuous fevers react least, those of an intermittent type being most amenable; and with these, again, the greatest effect is produced when the action falls in the period of the natural decline of temperature.

Sometimes antipyretics may even produce a "paradoxical action"—a rise in temperature.

2. The action on the remainder of the **central nervous system** consists in stimulation, followed by paralysis. We can distinguish a narcotic, a convulsant, and a collapse effect, these passing insensibly into each other.

(A) A slight **narcosis**—a diminished sensibility to pain and a certain degree of somnolence—may be seen with all antipyretics, and enhances their usefulness.

It is not understood in what way this is produced. It is not very large with ordinary doses, and these can not well be exceeded for fear of the collapse action. In *lactophenin* alone is it strong enough to produce a typical narcosis in doses in which there is no danger of collapse; and this drug might perhaps form a valuable substitute for morphin, since there is in no drug of this series any evidence of the establishment of a habit as with morphin.

(B) After the narcosis, and before the depression of the remainder of the central nervous system, come the **convulsant effects.**

The seat of these convulsions is probably diffuse, but they appear to start first in the brain. They are intermittent in character, and are preceded by increased reflex irritability.

(C) Following this there is *unconsciousness*, **collapse**, and, finally, total *paralysis*. The *pulse* is first accelerated, then slowed. The *respiration* becomes dyspneic and then diminished. There are sometimes vomiting and dilatation of the pupils. The skin is cyanotic and covered with cold sweat.

This collapse action is strongest in the mother substances—anilin, quinolin, phenylhydrazin, and carbolic acid, and generally in the members of the antiseptic group; so strong, indeed, that the action of these cannot be controlled, and they are hence unfit for internal administration.

Of the more usual antipyretics, acetanilid produces probably the strongest collapse effects; then come antipyrin, phenacetin, and lactophenin, in the order given.

Notwithstanding its insolubility, acetanilid has even been absorbed from wounds in sufficient amount to produce toxic symptoms.

This collapse—produced by large doses of the drugs themselves—must not be confounded with a collapse sometimes appearing after small doses in fever, and due, not to the drugs, but to the reduction of the temperature. We deal in these cases with a collapse which really pre-existed, but which was *masked by the hyperpyrexia*. An elevation of temperature produces effects in certain ways antagonistic to those of collapse, and may hide this condition. On removing the stimulus of the high temperature, the hidden collapse will of course become apparent. It would do so not only after the administration of antipyretic drugs, but also if the temperature were reduced by cold baths or any other means.

3. The **peripheral action** of the drugs is weak.

(A) They may produce some **local irritation** of the stomach, resulting in vomiting; but this action is much less pronounced than in the case of quinin.

(B) Nor is their action upon general protoplasm, their **antiseptic action,** very strong. They are, however, sometimes used as antiseptic dusting powders, and since they coagulate proteids, also form *hemostatics* (a 5% sterilized solution of antipyrin has been suggested). They have the advantage of being less poisonous and less irritating than iodoform.

(C) They have a peculiar effect upon the red corpuscles, leading to the formation of **methemoglobin,** and in larger doses causing a disintegration of the corpuscles (see p. 372).

These actions on the blood are much weaker than in the carbolic acid groups, and are weakest in antipyrin and its compounds. They lead to a peculiar cyanosis. The formation of methemoglobin by this group is much more pronounced inside of the body than in the shed blood.

(D) **Striped muscle** shows a somewhat increased efficiency on direct stimulation, and a weak curare action.

(E) **The heart** is first accelerated, and later slowed. This is due to direct action upon the heart muscle. The *vasomotor center* is not affected by moderate doses (with the exception of the part controlling the cutaneous vessels through the thermal centers). In consequence, the *blood pressure* depends solely upon the cardiac action, being at first increased and later diminished. In doses producing collapse there is paralysis of the vasomotor system, and consequent fall of blood pressure.

4. **Side-actions.**—The reduction of temperature by these antipyretics is apt to be accompanied by certain side-actions which may become dangerous if the dose be too large, or if the person be especially predisposed to them. They vary quantitatively to a considerable extent in different individuals, and even with the same person at different times. They may be referred for the most part to the central nervous system, the most frequent being *excessive sweating, chills, cyanosis, skin eruptions, digestive disturbances, symptoms resembling cinchonism, and collapse.*

The *sweating* is due to the increased circulation through the skin, and is produced in the same manner, and has the same significance, as the critical sweat of fever. It must be looked upon as beneficial rather than otherwise, since it aids the reduction of temperature. But should it become too troublesome, it can be suppressed by small doses of atropin.

The cutaneous hyperemia is probably also responsible for the *skin eruptions*. They are particularly frequent after antipyrin, especially when it has been used for some time.

The *chills* occur when the temperature begins to rise again, and are due to a diminished circulation through the skin, just as the chills of malaria. They are not, therefore, to be attributed to the drugs, but are rather a sign that the action of the antipyretic has worn off.

Gastric symptoms are due to local irritation, but are not frequent. *Cinchonism* symptoms are very rare, but have been reported. The *cyanosis* is due to the methemoglobinemia.

The *collapse* is the most dangerous complication. As has been said, this is usually due to the fall of temperature, and where there is reason for supposing the existence of such a masked collapse, when the fever is of a markedly asthenic type, great caution should be used in reducing the temperature, whether by drugs or by any other means. The production of collapse is most frequent in menstruating women. The cause of this is not understood.

It has often been stated that the antipyretics paralyze the *heart*. This is more than doubtful with ordinary doses. The belief probably resulted from the moderate slowing which is always produced, partly as a direct effect upon the heart muscle, but mainly as the result of the lowered temperature.

5. Dosage and Choice.—On account of the possibility of a direct collapse action if the *dose* is relatively large, the antipyretics must be administered with care.

In general, it may be said that, from the smallest effective dose (0.2 Gm. for acetanilid, 0.5 to 0.7 Gm. for antipyrin or phenacetin), the extent of the antipyretic action increases with the dose of the drug, until the normal temperature has been reached. Up to this point there is practically no danger of a direct collapse action. But if the dose necessary to secure this result be exceeded, the toxic effects will set in. As a *rule* for the actual dose to be employed, it is customary to give at the outset a total of 1 to 2 Gm. acetanilid, or 3 to 4 Gm. phenacetin, or 5 to 6 Gm. antipyrin, divided into two or three doses an hour or so apart. This causes a fall of 2° to 3° C.—*i. e.*, usually to normal—within three or four hours, and lasting for several hours. When the temperature begins to rise again, one-third of the above amount is repeated. Something like double the amount given above is required in the day to keep the patient practically fever-free. The action does not persist after the drug is excreted, and consequently the administration must be a continuous one, in the manner indicated. The comparative degree of toxicity of the different antipyretics has been given above (p. 357).

In regard to details, and in determining the *choice of the particular substance* to be used, experience is the best guide. The same holds here as in other cases. Very much more can be accomplished by any one drug that is thoroughly understood by the user, than can be done with a number of drugs with which he has had only limited experience.

6. Absorption and Excretion.—The coal-tar antipyretics are rapidly absorbed and excreted. They are for the most part decomposed in the body, or enter into paired combinations with sulphuric or glycuronic acid (see p. 373). Their oxidation products often give the urine a smoky color; the latter is also sometimes due to methemoglobinuria. After antipyrin, ferric chlorid gives a red color in the urine; after acetanilid, a reddish-brown color. The thallins cause a peculiar papillary nephritis.

The **toxicology** is not important. Toxic doses produce collapse, which is to be treated the same as collapse from other sources—stimulants, heat, etc. (see Aconite).

II. THERAPEUTIC USES.

We have already touched upon their slight *narcotic* and *local antiseptic action.* Their principal use is in the reduction of fever temperature. The entire therapeutics of fever may be summarized in this place.

Therapeutics of Fever.—The treatment of fever has always been tinctured by the views which have successively prevailed concerning its nature. When fever was considered mainly as a subjective condition, attention was directed principally to the sensations of heat and thirst, and there arose the class of *refrigerants*, including the dilute mineral acids (see Chap. XXVI, B). They are useful even now, especially carbonated drinks, in conjunction with other treatment. Since the alkalinity of blood is diminished in fever, the organic acids are also useful in this connection, in tending to make the blood more alkaline.

As physical observation came more into fashion, the quickened pulse of fever fixed the attention of the clinicians, and it was attempted to combat all the conditions of fever by slowing the pulse. The so-called class of *cardiac depressants* came into vogue. They include substances acting in various ways:

Aconite and *veratrin*, producing vagus stimulation and general collapse.

Digitalis, producing a slowed heart, but heightened blood pressure.

Nauseants, as tartar emetic, acting secondarily through the nausea.

Potassium salts, which have a direct action on the heart.

It does not need great acumen to perceive that remedies with actions so diverse could not be successful if employed indiscriminately in all cases of fever. Some have still a place in rational therapeutics, but only when used for special indications: *Aconite* offers advantages over the antipyretics if the fever is of a short high type; *digitalis*, if the heart is very irregular. Whether *nauseants* and *potassium* are ever indicated against fever, as such, is very doubtful.

When the thermometer was introduced into medicine, and it was recognized that an elevation of temperature was the best index to febrile conditions, *antipyretic measures* came into prominence.

The theoretically possible ways in which drugs may reduce temperature have been given on page 348. Practically, they are reduced to the following:

1. Lowering of the constant of the thermo-regulating center (coal-tar antipyretics).
2. Lowering of heat production by action on foci (quinin).
3. Dilatation of cutaneous vessels (with consequent diaphoresis) (aconite, nauseants, diaphoretics, alcohol).
4. Collapse action (aconite, veratrin).

To these could be added:

5. Removal of heat by mechanical means (cold baths, effusions, or pack).

Methods 2, 3, and 4 are discussed elsewhere.

In regard to the application of antipyretic measures in fever, it is essential to bear in mind that they have *no direct effects except upon the temperature.*

Exceptions to this general statement are the actions of quinin in malaria, of salicylates in acute articular rheumatism, and of cinnamic acid in tuberculosis.

For the rest, they strike neither at the cause of the fever nor at any symptoms other than those secondary to the hyperpyrexia. They make the type of the disease neither less severe nor shorter.

In malaria, for instance, they may prevent the development of a paroxysm of fever ; but they do not attack the cause of the disease as does quinin ; for their effect is not lasting, nor does their continued administration lead to a reduction in the size of the spleen.

They are a symptomatic and not a specific mode of treatment. And symptomatic treatment must always be carried on with great care, lest more harm than good should result. But where it is not possible to attack the cause, it is often advisable to remove objectionable symptoms. The question then is, *May a reduction of fever temperature be useful?* It must be borne in mind that hyperpyrexia is often a protective mechanism. This is shown by the onset of collapse in certain cases, if the stimulus of the high temperature be removed. Also, bacteriologic research has shown that with most bacteria the optimum temperature for development is confined within very narrow limits, which are exceeded by the temperature of fever. The *tendency* of fever may perhaps be said to be useful in all cases, but as a matter of fact it usually leads to more damage than good. The cells of the complicated mammalian organism are not adjusted to work under the conditions of so high a temperature. It is detrimental to them as well as to the bacteria, and sometimes more so. Its effects soon show themselves in the ways described in Chapter XVIII. They consist in lassitude and enervation, in general discomfort, restlessness, irritability, and delirium. The respiration and heart are quickened. The metabolism, and especially the elimination of nitrogen, is greatly increased. This leads to emaciation, diminished alkalinity of blood, degeneration of important organs, etc. All these, joined perhaps to a deleterious action of the increased metabolic waste-products, produce a condition highly detrimental to the patient. These conditions, in so far as they have not already passed into permanent anatomic changes, are promptly and totally removed by restoring the normal temperature. Measures for this purpose are therefore indicated whenever these symptoms arising from hyperpyrexia become very pronounced, and unless there are special contraindications. They should not be used, for instance, if there is ground for suspecting a masked collapse. Nor are they of any use in high continued fevers.

Antipyretic measures of this kind are mainly cold baths and the coal-tar antipyretics, and these have their respective drawbacks and advantages. The chief advantage of cold baths lies in the fact that there is no danger of a direct collapse action; but there is no need for this danger with antipyretics if their dose be properly adjusted. The latter save the patient the exertion, discomfort, and shock of a cold bath. As, in the case of baths, the temperature-regulating mechanism is not adjusted to normal, the patient experiences all the ordinary effects of an attempt to reduce the temperature below normal: chills, cyanosis, etc.; and the metabolism is increased rather than diminished. The action of the chemic antipyretics is also more pronounced and lasting (Fig. 66), and the narcotic action of some members is of marked value in influencing the subjective condition of the patient. In regard to this *narcotic action*, antipyrin and acetanilid are about on a level; they are surpassed by phenacetin, and still more by lactophenin. This action is especially useful when the fever is associated with pain, from whatever cause, or with delirium. It is probably also this narcotic action which makes the drugs useful in *neuralgia*, *headache*, and *migraine*. "Migrainin" consists of: Antipyrin, 85; caffein, 9; citric acid, 6.

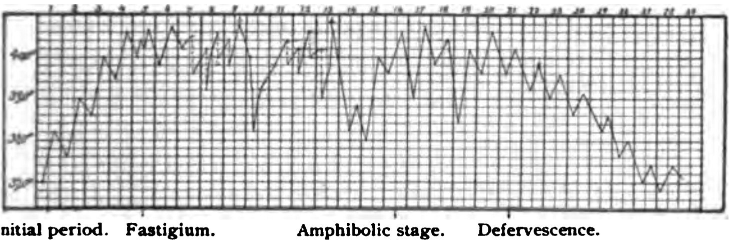


Fig. 66.—Antipyretics in typhoid fever. Dotted lines = cold baths; + = antipyretics (Strümpell).

The addition of caffein to the antipyretics would always be useful, to counteract the tendency to collapse or to a cardiac action; and the addition of bromids is also useful to heighten the narcotic action.

III. MATERIA MEDICA.

⁎*⁎ *Acetanilidum* (U.S.P., B.P.).—(*Antifebrin Phenylacetamid.*) C_6H_5-$NH(CH_3CO)$. Prepared by boiling anilin with glacial acetic acid and crystallizing:

$$C_6H_5NH_2 + CH_3CO_2H = H_2O + C_6H_5NH(CH_3CO)$$

Soluble in 200 parts of cold water, and in 5 parts of alcohol. *Dose:* to 0.5 Gm. (8 grs.); per day, to 4 Gm.; in powders or capsules.

All the other antipyretics are unofficial. With the exception of antipyrin, which is very soluble, they are practically insoluble in water, and are given in powder form or as cachets, in *doses* of 0.3 to 0.6 to 1.0 Gm. (5 to 10 to 15 grs.). We will enumerate a few of the more common:

⁎*⁎ *Antipyrin* [*Phenazonum*, B.P.] = $C_{11}H_{12}N_2O$. = Dimethyloxyquinin (Analgesin).

⁎*⁎ *Phenacetin* (B.P.) = $C_{10}H_{13}NO_2$ = Para-acet-phenetidin.

⁎*⁎ *Lactophenin* = $C_{11}H_{14}NO_4$ = Lactyl-phenetidin.

**Phenocoll* = $C_{10}H_{14}N_2O_2$ = Amido-aceto-phenetidin.

**Salophen* = $C_{15}H_{13}NO_4$ = Acetyl-paramido-phenyl Salicylate.

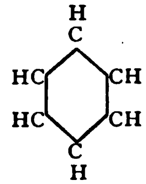
**Exalgin* = $C_9H_{11}NO$ = Methyl acetanilid.

**Benzanilid* = $C_{13}H_{11}NO$ = Benzoyl-anilid.

**Thallin Salicylate* = $C_{10}H_{13}NO.C_7H_6O_3$.

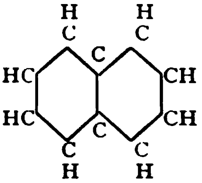
Various mixtures, usually consisting of acetanilid, caffein, and sodium carbonate, are found on the market under fancy names.

IV. CONSTITUTION OF SOME PHARMACOLOGICALLY IMPORTANT COAL-TAR DERIVATIVES.[1]



= *Benzol* C_6H_6

$C_6H_5CH_3$ = *Toluol*
$C_6H_4(CH_3)_2$ = *Xylol*

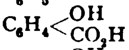


= *Naphthalin* $C_{10}H_8$

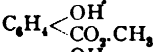
Oxybenzols: $C_6H_5.OH$ = *Phenol*
$C_6H_4(OH)_2$ = *Resorcin*
$C_6H_3(OH)_3$ = *Pyrogallol*
$C_{10}H_7.OH$ = *Naphthol*

$C_6H_3.CH_3.CH_3O.OH$ = *Creosol*
$C_6H_3.CH_3.C_3H_7.OH$ = *Thymol*
$C_6H_4.OH.OCH_3$ = *Guaiacol*
$C_6H_4.OH.CH_3$ = *Cresol*

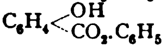
Aromatic Acids: $C_6H_5.CO_2H$ = *Benzoic Acid*
$C_6H_5.CH.CH.CO_2H$ = *Cinnamic Acid*



$C_6H_4<^{OH}_{CO_2H}$ = *Salicylic Acid*



$C_6H_4<^{OH}_{CO_2.CH_3}$ = *Oil of Wintergreen*



$C_6H_4<^{OH}_{CO_2.C_6H_5}$ = *Salol*

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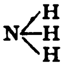
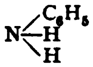
[1] Small capitals = Antipyretic group; italics = antiseptic group.

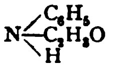
* Unofficial.

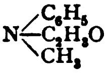
The most important drugs are marked ⁎*⁎.

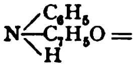
Nitrogen Derivatives:

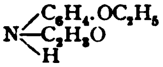

$N\left\langle\begin{matrix}H\\H\\H\end{matrix}\right.$ = Ammonia

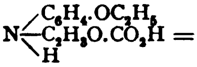

$N\left\langle\begin{matrix}C_6H_5\\H\\H\end{matrix}\right.$ = *Anilin*

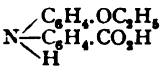

$N\left\langle\begin{matrix}C_6H_5\\C_2H_3O\\H\end{matrix}\right.$ = ACETANILID

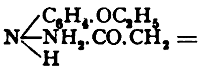

$N\left\langle\begin{matrix}C_6H_5\\C_2H_3O\\CH_3\end{matrix}\right.$ = EXALGIN


$N\left\langle\begin{matrix}C_6H_5\\C_7H_5O\\H\end{matrix}\right.$ = BENZANILID


$N\left\langle\begin{matrix}C_6H_4.OC_2H_5\\C_2H_3O\\H\end{matrix}\right.$ = PHENACETIN


$N\left\langle\begin{matrix}C_6H_4.OC_2H_5\\C_2H_3O.CO_2H\\H\end{matrix}\right.$ = LACTOPHENIN


$N\left\langle\begin{matrix}C_6H_4.OC_2H_5\\C_6H_4.CO_2H\\H\end{matrix}\right.$ = SALOPHEN


$N\left\langle\begin{matrix}C_6H_4.OC_2H_5\\NH_2.CO.CH_2\\H\end{matrix}\right.$ = PHENOCOLL

$C_6H_5.NH.NH_2$ = *Phenylhydrazin* $C_6H_5(CH_3)_2C_3HN_2OH$ = ANTIPYRIN

Naphthalin Derivatives: $C_{10}H_8$ = *Naphthalin*
C_9H_7N = QUINOLIN
$C_9H_6.OCH_3.NH_4$ = THALLIN
$C_9H_6.CH_3.NH_4O_2$ = KAIRIN

(B) ANTISEPTIC GROUP.

The second coal-tar group, that of the *antiseptics*, is characterized by the prominence of the toxic action on protoplasm when brought into direct contact, and of the collapse action when acting from the circulation.

I. MEMBERS.

The group comprises most of the aromatic compounds not enumerated under antipyretics, viz.:

The mother-substances: Benzol itself, Naphthalin, Anilin, Quinolin, Pyridin, etc.

The hydrates; Phenol, Naphthol, Resorcin, Hydrochinon, Pyrocatechin, Pyrogallol, Salol, Thymol, Guaiacol, Cresol, and Creosol.

The acids: Salicylic, Benzoic, Cinnamic.

Oil of Wintergreen.

Most of the anilin dyes, etc.

In this group belong, further, a number of natural mixtures:

Wood-tar, containing chiefly guaiacols, creosols, carbolic acid, and cresols; also some acetic acid.

Creosote, a product obtained by the distillation of beechwood, contains chiefly guaiacols and creosols. Wood-smoke also contains these bodies, and owes to them its antiseptic and preservative properties.

The aromatic balsams—Balsam of Peru and Copaiba, Styrax, Tolu, Benzoin, etc.—also owe their activity largely to members of this series; benzoic and cinnamic acid, etc.

Ichthyol, a product of the distillation of a certain bituminous shale, also seems to belong here, although its constitution is not well understood. It is characterized by a high content of sulphur.

Historical.—In the form of the natural mixtures, the antiseptic properties of this group have long been known. The smoking of meat is certainly a very ancient practice; and one of the methods of embalming practised by the Egyptians utilized largely balsams and products rich in essential oils,—the latter being very closely related to the aromatic series. The isolated substances, however, belong to the achievements of the nineteenth century. Creosote was first made in 1832, carbolic acid in 1834, and it was almost thirty years later than this before they were used in surgery.

II. SUMMARY OF ACTIONS.

1. A coagulating action upon proteids, determining the death of cells with which they come in contact, and resulting in irritation and inflammatory changes.
2. An excitation, followed by more pronounced depression, of the central nervous system.
3. The formation of methemoglobin.

III. DETAILS OF ACTION.

1. **Local Actions.**—Most of the members of this group coagulate, and thus destroy the structure of, proteids, and, in consequence, of protoplasm.

This action, which exists only to a very slight extent in the antipyretic group, is strongest with *carbolic acid*; and since this also exhibits the other properties of the series in the most typical manner, the following description is meant to apply mainly to this substance. The special properties of the other members, in so far as they are of practical import, will be summarized later.

When pure carbolic acid, or a strong solution of it, is applied to the skin or mucous membranes, it acts as a caustic. It produces burning and pain, then numbness and anesthesia, wrinkling and softening of the epidermis, the color of the skin becoming first white, then red, and finally brown. A dry scab forms, which separates without pus. Creosote has a similar but much weaker action. In weaker solutions neither is caustic, and they determine merely some wrinkling and blanching of the epidermis. But even a 5% solution of the acid may cause necrosis, especially when applied continuously to the extremities. This enjoins caution in the use of carbolic dressings. Ninety-five per cent. alcohol is said to be antidotal to the local effects of carbolic acid. None of the other members of the group have such a marked caustic action, although salicylic acid effects a softening of the epidermis, which leads to its use in removing corns. It is important to note that its salts, the salicylates, have no caustic action, but are nevertheless antiseptic. All the members have, however, some local action, which finds its expression, with internal administration, in *nausea, vomiting, and diarrhea*, being similar to quinin in this way. The vomiting is also favored by the repulsive taste of some of these drugs. This local irritant action further shows itself after large doses at the place of excretion—*e. g.*, in *nephritis* with casts, albuminuria, and hemoglobinuria. (Fig. 67.) *Skin eruptions* which occur occasionally may be ascribed to this irritation and to the dilatation of the cutaneous vessels. Strong solutions brought into direct contact with a muscle, decrease its excitability. The coagulant action on proteids also determines the most characteristic property of the group, namely, their *antiseptic effects*.

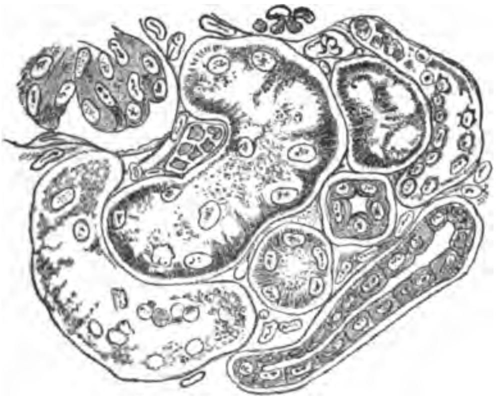


Fig. 67.—Rabbit's kidney after salol-poisoning (Kobert).

This coagulation is a molecular, rather than a chemic, process. That is to say, phenol and the other drugs of the group do not enter into chemic combination with the proteids, but precipitate them by changing the character of the *medium*, somewhat after the manner of alcohol or neutral salts. A short action of this kind is sufficient to kill the protoplasm. But the coagulant substance itself, not being combined and used up in this process, is free to penetrate further, which is not the case with the metallic antiseptics. This penetration is also favored, in the case of carbolic acid, by its volatility, a factor which is absent with salicylic acid and most other members of the group. The metals enter into insoluble, permanent, chemic combination with the protoplasm, and this effectually prevents the further penetration of the antiseptic. This greater penetrating power of the antiseptics of the aromatic group is of considerable practical importance. Further, just as different proteids present different degrees of precipitability with alcohol, ether, and chloroform, or with the different neutral salts, so they are acted upon differently by the various members of this series; and this suggests the explanation of the fact that different bacteria present a very different degree of resistance to them; and that certain members may be almost specific in a disease—as salicylic acid in acute rheumatism—where the other members are of but very little use.

It is claimed that carbolic acid is curative in *traumatic tetanus*. For this purpose a 2% solution is injected every two to three hours, beginning with 0.2 Gm. of the pure acid (or 10 c.c. of the solution) per day, and increasing rapidly to 0.5 Gm. The results require further proof.

The *anilin colors* appear to have some antitoxic powers if they are mixed with toxins before injection; but it is very doubtful whether they can exert this in the organism.

Carbolic acid *prevents putrefaction*, or the development of bacteria, in the strength of ½ to 1%.

For the production of surgical antisepsis, too much stress must not be laid upon the fact that it does not kill the organisms in even much greater concentration; for the prevention of their growth is all that is required in the treatment of open wounds.

The use of these drugs as antiseptics will be further discussed on page 374.

They also have a retarding effect upon *ferment action*—especially carbolic and salicylic acid—somewhat after the manner of quinin. A 5% solution of phenol suffices to materially weaken the action of most ferments.

2. Central Actions.—The action upon the *central nervous system* presents a close analogy with that of the antipyrin group, with the important difference that collapse is produced much more readily, and that it is much more difficult to adjust the doses in such a way as to get a desired effect without the admixture of a more or less violent collapse action. They present the same primary *narcotic* effect on frogs as was noted with the antipyretics. The following symptoms of *excitation* are more pronounced, and are shown in frogs or mammals by muscular tremors, twitchings, and convulsions.

Carbolic acid causes in the frog a short stupor, followed by incoordinated clonic convulsions. The latter involve the entire central nervous system. Intactness of the sensory paths is necessary for their production, so that they, like those of strychnin, rest upon an increased excitability. The action differs from that of the latter poison in its wider distribution, and in the more incoordinated spasms.

There are also signs of stimulation of the medullary centers, especially that of *respiration*. The *heart* is quickened, probably by a direct action on the cardiac muscle. The *blood pressure* consequently rises.

These stimulant effects are shown only if the carbolic acid be slowly absorbed. If it is injected into the circulation or absorbed rapidly for any reason, the *collapse* sets in before there is time for the development of convulsions or other stimulations.

In the collapse stage the *heart* is weakened and slowed —presumably by direct action on the muscle. There is *paralysis of the vasomotor center*, and in consequence *fall of blood pressure* (Fig. 68, *B*). The *respiration* becomes slow and shallow, and finally ceases. The *temperature* falls. The phenomena bear a very close resemblance to those of surgical shock. Since the collapse affects all the medullary centers, and the cardiac muscle as well, it cannot, of course, be removed by artificial respiration. This constitutes an important difference to the collapse produced by the drugs of the alcohol series. Another difference consists in the fact that with the antiseptic group the *sensibility to pain* is often *preserved* far into the collapse. In an early stage there is a *mental excitation* with hallucinations, seen especially with salicylic acid. The collapse action is strongest with carbolic acid and creosote, much less with salicylic acid, and very small with benzoic acid.

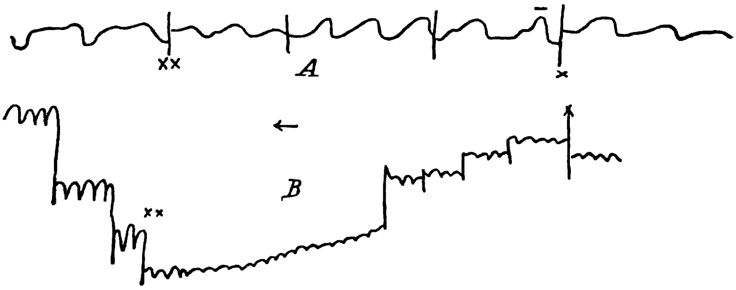


Fig. 68.—Carbolic acid (begins at ×) and sodium sulphate (begins at ××). Dog. *A*, respiration (from tracheal cannula); *B*, carotid pressure. The pressure indicates vasomotor paralysis. This and the dyspnea are at once relieved by sodium sulphate.

Of further actions of the carbolic acid group referable to the nervous system, must be mentioned the effect on the *thermo-regulating center*, after the manner of the antipyrin group (dilatation of the cutaneous vessels). This is overshadowed by the collapse action, and is utilized only with salicylic acid. There is an increase of *secretions*, especially of saliva, sweat, and tears, not yet accounted for. Symptoms of *cinchonism* also sometimes make their appearance after carbolic and especially salicylic acid. Their pathology is the same as with quinin (p. 346). Peripherally, *muscle- and nerve-fibers* are killed by the direct application, but do not seem to suffer when the drugs act systemically. Carbolic acid is of value as a *local anesthetic* (5% ointment), especially in itching skin diseases or pruritus.

The production of methemoglobin will be considered on page 372.

IV. TOXICOLOGY.

This is of considerable importance, since carbolic acid is so easy of access. Accidental and suicidal poisoning by it is extremely common.

It is rapidly absorbed, even from the *intact skin*, and its use on open surfaces has frequently led to toxic symptoms. The *minimum fatal dose* may be stated as about 10 to 15 Gm. (150 to 225 grs.).

Symptoms.—These depend upon the concentration in which the drug has been taken. If *pure* or in very strong solution, it may produce almost *immediate collapse* through its *local action*, after the manner of mineral acids (see Chap. XXVIII, A). When *large doses of dilute acid* are taken, the collapse may also occur without other symptoms, in this case from its action on the central nervous system. With moderate but fatal doses the *typical symptoms* are: Burning in mouth and throat; nausea and vomiting; faintness and muscular weakness; sometimes twitchings and convulsions; pulse small, weak, and slow; face livid; cold sweat; respiration slow and shallow; unconsciousness; coma; death by stoppage of respiration.

Chronic Carbol-poisoning.—In the days of the Lister spray, chronic phenol-poisoning was not at all uncommon amongst surgeons. It presented the general symptoms of marasmus. The quantity of the acid entering the system under these circumstances is quite phenomenal: 2 Gm. of phenol were recovered from the urine of a surgeon who had assisted for two and a half hours at an operation under a 2% spray.

The course of carbolic acid poisoning is *very rapid.* In almost all fatal cases death ensues inside of twenty-four hours.

Diagnosis.—Besides the course of the symptoms noted, the *odor* of the patient is characteristic. The *urine* is dark and smoky, and gives little or no precipitate with *barium chlorid.* The carbolic acid usually exists in the urine combined with sulphuric or glycuronic acid, and is free only in the very gravest cases. To demonstrate its presence by chemic tests, the urine must be *acidulated and distilled*, and the distillate tested (see p. 100).

Treatment.—This should be directed mainly to the speedy removal of the acid and to efforts to render it harmless by chemic means. The stomach-pump is the best means for the former purpose, and *lime-water* is best for the lavage, since it precipitates the acid. *Syrup of lime* may be given as antidote for the same purpose. *Sodium sulphate* should also be administered; it has the double purpose of hurrying the unabsorbed acid through the intestine, and a part is absorbed and forms sulphocarbolates which are not so poisonous (Fig. 68). In serious cases no reliance should be placed upon its absorption from the alimentary canal, but it should at once be injected hypodermically. The prompt administration of alcohol has been strongly recommended. The rationale of its action is not clear.

The *collapse symptoms* should be met by *medullary stimulants*, ammonia holding first place.

Sulphocarbolates are less poisonous than carbolic acid. The crude products —tar and creosote—agree with carbolic acid, and are used only as antiseptics.

V. SALICYLIC ACID.

The action of salicylic acid is shared by its salts—the salicylates; by oil of wintergreen (methyl-salicylic ester); by its compounds with various aromatic bodies (betol, thymol- and guaiacol-salol, salophen, salol, etc.), and salicin. Most of these yield salicylic acid in the body. *Salol* is decomposed in the intestine, yielding salicylic and carbolic acid, a fact of some importance, since the collapse action of the latter must be borne in mind. *Salicin* is a glucosid which also eventually yields salicylic acid.

The nauseant taste of the salicylates cannot be thoroughly disguised by any flavors, and they produce considerable nausea and gastric irritation, which interfere with their use. This unpleasant property appears to reside in the (OH) radicle. If this is replaced by methyl they disappear—but so do the antiseptic qualities. The sodium-acetyl-salicylate—*aspirin*—is also devoid of the taste and primary irritation, but it is gradually, though completely, decomposed in the blood, with liberation of salicylates, so that it is almost fully as active, therapeutically, as the latter. It also does away with the cinchonism.

Differences from Carbolic Acid.—The effects of salicylic acid differ from those of phenol by a *lesser action on the central nervous system.* The *convulsive action* is almost nothing, and the collapse action much weaker than with carbolic acid.

The antiseptic effects differ from those of phenol by the *lesser penetration* on account of the non-volatile nature of the substance. The *irritant effects* are weaker, except in the case of the free acid. However, all salicylates have a *nauseant taste* and produce considerable gastric irritation.

Injected intravenously into animals, methyl and ethyl salicylates cause pulmonary edema through injury to the capillary walls.

In addition, the salicylates cause somewhat increased secretion of *urine*, perhaps by their irritant action on the kidney cells. The *bile* is similarly increased, and salicylates and bile are the only true cholagogues known (see Chap. XXX). The N, especially in the form of urea, is increased, and this increase is so lasting that it must be due to a breaking up of proteids, and not simply secondary to the diuresis. It does not affect the *absorption of fat or proteids.*

The treatment of salicylic acid poisoning is entirely symptomatic. The principal use of salicylates is in the treatment of *acute rheumatism*, when they are almost specific. They are given in gram doses, dissolved in water, every hour or two as long as the stomach will bear them. Oil of wintergreen is also used locally near the affected joint. It acts largely as a counterirritant, but it is not inconceivable that enough may be absorbed, in virtue of its volatility, to exert the specific action. The salicylates have very little action in chronic rheumatism or gout. If used at all for this purpose, they are given in the form of salol (2 Gm. per day).

None of the other members of the series is given internally, for any purpose but antisepsis, and they will be considered under that heading (see p. 374).

Pyrogallol, however, has a special interest on account of the *methemoglobin formation*, which is produced to some extent by all members of the group, but most intensely by it. Concentrated solutions acting on blood outside of the body produce a peculiar insoluble substance—*hemogallol*. This is never formed in the body; here, and with *dilute solutions* in vitro, the corpuscles become shrunken, crenated, and fragmented, and lose most of their hemoglobin. The latter is partly changed into methemoglobin. The *symptoms* in the case of pyrogallol are for the most part consequences of this process. It leads to icterus, hemoglobin- and methemoglobin-uria, and a more or less violent nephritis, if the disorder runs a slow course; or cyanosis, dyspnea, and convulsions, if the course is rapid. The *treatment* of poisoning must be symptomatic; large injections of normal salt solution would be indicated.

VI. METHEMOGLOBIN-FORMERS.

Methemoglobin has the same elementary composition as oxyhemoglobin, but the two differ very essentially in certain of their properties:

1. The spectrum (see figure 71, Chap. XXI, B). The color of methemoglobin has more of a brownish tinge.

2. In the readiness with which they give up oxygen. Whilst the oxyhemoglobin is a very unstable compound, giving up its oxygen and taking it again, with great readiness, methemoglobin is a comparatively stable and unchangeable compound.

3. In their behavior to certain reagents. For instance, HCN does not form any characteristic compound with oxyhemoglobin, but with the methemoglobin it gives cyanmethemoglobin. Similar compounds are formed with H_2O_2, sulphocyanids, and many other salts.

Methemoglobin may be formed from oxyhemoglobin in quite a number of different ways (see Chap. XXXIII):

1. By oxidizing agents: $KClO_3$; Pot. ferricyanid; Pot. permanganate, H_2O_2, etc.
2. By reducing agents: The nitrites, hydroxylamin, etc.; coal-tar products. (Phenylhydrazin also gives reduced hemoglobin.)
3. By acids and iodin; also in the early stages of putrefaction.
4. By salts and glycerin.

The physiologic significance of this methemoglobin formation rests on the stability of the compound, and its consequent inability to carry out the functions of oxyhemoglobin. This produces asphyxia of the tissues Pure methemoglobin solutions may be injected into the blood, without causing any symptoms. Even the urine remains free from albumin or methemoglobin. The compound is in part secreted by the bile, in part deposited in the hematopoietic organs.

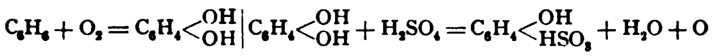
Nor is the *temporary* conversion of a considerable proportion of the oxyhemoglobin into its isomer of great significance; for methemoglobin is not absolutely stable, and as soon as the oxygen-starvation of the tissues is carried to a certain degree, they seize upon the methemoglobin and decompose it. The condition can therefore become dangerous only if the methemoglobin-former continues its action. This does not occur in therapeutic doses of any of these drugs, but may contribute to the fatal ending in cases of poisoning. The symptoms are those of asphyxia. There is a peculiar blue about lips and finger-nails, etc. The methemoglobin gradually returns to oxy- or reduced hemoglobin after death, so that an examination after several days may fail to reveal its presence.

Many of these agents cause, in addition, a breaking up of the corpuscles, and this greatly increases the danger. Aside from the asphyxia which must be proportioned to it, the proteid and other substances liberated cause injury to the kidney—albuminuria, glycosuria, methemoglobinuria, etc. It is also claimed that it causes the sudden formation of fibrin ferment, which may then cause extensive intravascular clotting. The debris is also credited with causing emboli. But these facts are not admitted by all authorities. A small destruction, such as may be caused by the subcutaneous injection of glycerin, certainly has no permanent injurious effect.

The specific action of the drug is, of course, joined to these methemoglobin effects, and may entirely overshadow them. Thus, rabbits die of $KClO_3$ before it comes to any methemoglobin formation.

VII. FATE OF THE COAL-TAR DERIVATIVES IN THE BODY.

The aromatic compounds tend to undergo oxidation in the body; but this affects in almost all cases the hydrogen atoms or side-chains only, leaving the carbon atoms of the ring intact, and preserving the form of the latter. The result is hydroxyls or acid groups. These new compounds again enter into combinations,—those containing hydroxyl groups with sulphuric and glycuronic acids; those containing acid radicles with glycocoll. A few formulas will illustrate this:



$$\underset{\text{Benzol}}{C_6H_6} + O_2 = \underset{\text{Dioxybenzol}}{C_6H_4{<}{\begin{smallmatrix}OH\\OH\end{smallmatrix}}} \Big| \; C_6H_4{<}{\begin{smallmatrix}OH\\OH\end{smallmatrix}} + H_2SO_4 = \underset{\textit{Phenol-sulphuric Acid}}{C_6H_4{<}{\begin{smallmatrix}OH\\HSO_3\end{smallmatrix}}} + H_2O + O$$

$$\underset{\text{Carbol}}{C_6H_5.OH} + \underset{\text{Glycuronic Acid}^{1}}{HCO_2.(CH.OH)_4.COH} = \underset{\text{Phenol-glycuronic Acid}}{C_6H_5.CO_2.(CH.OH)_4.COH} + H_2O$$

$$\underset{\text{Salicylic Acid}}{HC_7H_5O_3} + \underset{\text{Glycocoll}}{C_2H_5NO_2} = \underset{\text{Salicyluric Acid}}{HC_9H_8NO_4} + H_2O$$

$$\underset{\text{Benzoic Acid}}{HC_7H_5O_2} + C_2H_5NO_2 = \underset{\text{Hippuric Acid}}{HC_9H_8NO_3} + H_2O$$

There are considerable differences in detail; other products are formed along with those given, such as hydrochinon, pyrocatechin, etc., whose oxidation products give rise to the characteristic dark color.

The formation of these combined acids is of considerable practical importance. They are much less poisonous, and their production is in that measure a protective mechanism, whose efficiency can be increased by the administration of soluble sulphates (see p. 371). They also form an index to the gravity of the poisoning. The phenol sulphates do not precipitate with Ba, and hence so long as the urine gives a precipitate with the latter, it is a certain indication that the organism is able to cope with the poison. But when the precipitate becomes very small or disappears, the sodium sulphate should be pushed rapidly. These compounds also reduce copper, and may therefore be mistaken for sugar.

The principal ***drugs which cause the appearance of reducing substances***, not sugar, ***in the urine*** are: Turpentine, chloroform, chloral, phenacetin, saccharin, salicylic acid, balsams.

(C) DISINFECTION.

I. GENERAL CONSIDERATIONS.

Toxicity and Resistance.—Passing now to the main use of the second group—that of the antiseptics—it is well to discuss the whole subject of chemic disinfection in this place.

The number of substances which are capable of destroying bacteria or inhibiting their growth is very large. We are dealing here with minute isolated particles of living protoplasm, and it is well known how delicately sensitive the latter is to changes in its environment. Almost any pronounced change in the latter will be detrimental to the former. Thus, it is only necessary to increase the percentage of soluble matter—salts or sugar—in the medium above a certain point to cause coagulation of the globulins, etc.; and, in addition, certain other substances have a more specific toxic effect (an ion action), even in minute doses.

On the other hand, the bacteria are endowed with a peculiar resistance to such influences, due perhaps to a mechanism preventing the thorough penetra-

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[1] Glycuronic acid is derived from sugar as follows:

$$CH_2OH — (CH.OH)_4 — C^{O}_{H} = \text{Glucose}$$

$$COOH — (CH.OH)_4 — C^{O}_{H} = \text{Glycuronic Acid}$$

tion of the reagents; to a resistant cell-wall. This mechanism is rendered still more efficient by the property of spore formation, in which an extremely impenetrable cell-wall is developed. Consequently, whereas it is a comparatively easy matter to so alter the medium as to render it unfit for the development of bacteria, it is a much more difficult one to kill them outright. Change in the medium is sufficient for the former, but penetration is required for the latter. As a matter of course, if the medium is rendered unfit for the organisms, so that they cannot grow nor reproduce in it, they will eventually die; but since many bacteria, and especially their spores, are endowed with a remarkable property of remaining for a considerable time dormant but alive under unfavorable conditions, and again developing when these are more favorable, a practical distinction must be made between *antiseptic* and *germicidal* action,—the former hindering the development of the organisms, the latter killing them outright. All germicidal substances are, of course, antiseptic, but the converse does not always hold true, as for instance in the case of salt or sugar. A third class may also be considered in this connection—the *deodorants*—which destroy some of the odorous bacterial products, but not the bacteria themselves.

Factors Determining Usefulness.—The nature of the antiseptic substance, or the strength in which it is used, are by no means the only factors determining its efficiency and usefulness. Amongst the other more important factors may be mentioned:

1. The *nature of the micro-organism.*

Saprophytes are more resistant than pathogenic bacilli; micrococci than either, and spores most of all.

There also is some *selective action*, some substances being comparatively much more toxic to one species than to another. (Thus, gold chlorid is more toxic to anthrax than to cholera; carbolic acid, the reverse.)

2. The *number of bacteria to be destroyed.*

3. The *nature and quantity of the associated material.* Many substances which are strongly germicidal when acting on the bacteria alone are much weakened by entering into chemic reactions with the medium.

Thus, potassium permanganate is *destroyed* by all organic matter; mercuric chlorid is *precipitated* by proteids; silver nitrate by chlorids, etc. These insoluble combinations are no longer germicidal. Further, they *hinder the penetration* of the antiseptic, a condition of considerable surgical importance. Of all the antiseptics, those of the aromatic series are least acted upon. As we have seen, they do not enter into chemic combination with the media, and have therefore a superior penetrating power.

4. The *time of exposure.* The different antiseptics show great variations in this.

5. The *degree of dilution* of the disinfecting agent is in most cases of the greatest importance. A decigram of sublimate in 100 c.c. of water will be much more efficient than a gram in ten liters.

6. The *toxic and corrosive action* of the agent, and the ease with which it is absorbed, are also often of importance in deciding its practical usefulness.

7. The *cost* often enters into consideration.

II. ANTISEPTICS IN COMMON USE.

The more commonly used antiseptics are the following:

Inorganic Salts: $HgCl_2$, $AgNO_3$, $FeSO_4$, $CuSO_4$, $ZnSO_4$, $ZnCl_2$, Al_2Cl_6, $K_2Al_2(SO_4)_4$, NaCl, KI, NaFl.

Acids: H_2SO_4, HNO_3, $HC_2H_3O_2$, H_3BO_3, As_2O_3.[1]

Alkali: CaO.

Oxidizing and Reducing Bodies: SO_2, $KMnO_4$, H_2O_2, O_3, I, Br, Cl, Calx Chlorata.

Fatty Series: $CHCl_3$, CHI_3, CH_2O, C_2H_5OH, $C_3H_5(OH)_3$, sugar.

Aromatic Series: See Materia Medica, page 387, and table, page 364. To this may be appended camphor and the essential oils.

Alkaloid: Quinin.

Manner of Action.—Of the inorganic salts, those of the *heavy metals* and of *aluminium* are antiseptic by forming insoluble proteid compounds with the protoplasm of the bacteria. However, they do not probably penetrate the cell-wall very readily, and their action is certainly a very slight one,—unless they possess a specific toxicity, as does mercury. In all cases their action is very greatly weakened if other proteids are present, as they are bound and rendered inactive. The greater number are deodorant, rather than antiseptic, by combining with the H_2S and NH_3 and similar odorous substances.

Of the *neutral salts of alkalies*, the *fluorids*, and to a less extent the *borates*, possess specific toxicity. The effects of NaCl and KNO_3, as also sugar, are due purely to salt action. They render the medium unfit for the bacteria and thereby lower their vitality. The *iodids* have no special action, except when iodin is liberated from them.

Bacteria, like all living organisms, require a certain *reaction* of medium for their development; and a considerable modification of this, by either acids or alkalies, is inimical to them. Most forms are more sensitive to the former than to the latter.

Strong *oxidizers and reducers* tend to produce chemic changes in all organic matter, and bacteria are no exception. However, for this very reason these substances are quickly rendered inactive by any foreign matter which is usually found with these organisms. It can never be hoped to have any action from them after their absorption; and locally only if the amount of organic matter present is small; or apart from the body, if they can be used in sufficient concentration without also destroying the infected article.

The drugs of the *fatty series* are rather weakly antiseptic; for their action lies in the precipitation of protoplasm produced by them. Since these precipitates remain capable of being dissolved for a considerable length of time, they are scarcely at all germicidal.

Table XIV will serve to give some idea of the *relative strength of these antiseptics*, if it be borne in mind that these figures cannot be applied indiscriminately to all bacteria.

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[1] Arsenic is an insecticide rather than a germicide.

TABLE XIV.—DISINFECTING POWER OF COMMONLY USED ANTISEPTICS.[1]

St = Sternberg; M = Miquel; K = Kitasato.

	Antiseptic: Prevents permanently the putrefaction of bouillon inoculated with sewer bacteria.	Germicidal		
		to Anthrax Spores.	to Typhoid Bacilli.	
$HgCl_2$ . . .	1 : 15,000 (M)	: 1,000 few min. (Koch) : 10,000, two hours (St)	: 10,000 two hours (Frånkel)	
$AgNO_3$ . .	1 : 12,000 (M)	: 4,000	. .	
$FeSO_4$ . . .	1 : 90 (M)	not	not	
$CuSO_4$ . . .	1 : 110 (M)	. .	: 100, two hrs. : 20, ten min. (Leitz)	
$ZnCl_2$ . . .	1 : 500 (M)	. .	. .	
Al_2Cl_6 . .	1 : 720 (M)	. .	. .	
$AC_2K_2(SO_4)_4$	1 : 222 (M)	. .	. .	
H_2SO_4 . .	1 : 800 (St)	not	: 1,550, 24 hours (Boer)	
$HC_2H_3O_2$.	1 : 250 (K)	not	: 330, 5 hours (K)	
H_3BO_3 . .	1 : 143 (M)	not	: 300, 5 hours (K)	
As_2O_3 . . .	1 : 166 (M)	: 100, ten days (Koch)	. .	
CaO . . .	1 : . .	. .	: 1,000, five hours (K)	
SO_2	1 : positive	not	positive	need moisture
$KMnO_4$ . .	1 : 285 (M)	: 20, one day (Koch)	. .	
H_2O_2 . . .	1 : 20,000 (M)	: 125, 2 hours (St)	. .	need moisture
Br	1 : 1,666 (M)	: 50, twenty-four hours (Koch)	. .	
Cl	1 : 4,000 (M)	: 100, 3 hrs. (Fisher)	. .	
Calx chlorata	1 : . .	: 100, two hrs. (Boer)	: 2,000, 2 hrs. (Boer)	
$CHCl_3$ . . .	1 : . .	not	: 200, 1 hour (Kirchner)	
CHI_3 . .	1 : positive	not	. .	
Formaldehyd (absolute)	1 : 5,000 (checks development of typhoid)	. .	. .	
C_2H_5OH . .	1 : 333 (M)	: 33, two days (Koch)	: 100, 2 hours (Bolton)	: 1,000 aureus (Slater and Rideal)

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[1] The results of the observations of different experimenters are not comparable, since the proteid content of the solutions is not uniform.

Disinfecting Power of Commonly Used Antiseptics.—(*Continued.*)

	Antiseptic: Prevents Permanently the Putrefaction of Bouillon Inoculated with Sewer Bacteria.	**Germicidal**		
		to Anthrax Spores.	to Typhoid Bacilli.	
Glycerin	1 : 4 (M)	not	..	
Carbolic acid	1 : 333 (M)	: 33, two days (Koch)	: 100, 2 hours (Bolton)	
Creosote	1 : 3,0 0 (Gutmann)	..	..	: 300, pyocyaneus, 1 min.
Creolin	1 : 5,000	..	..	
Trikresol	1 : 1,000	..	..	
Salicylic acid	1 : 1,000 (M)	not	: 70, five hours (K)	
Benzoic	1 : 900 (M)	not	not (K)	
Pyoktanin	1 : 2,000 (Boer, typhoid)	not	: 1,000, thirty minutes (Jaencke)	
Thymol	1 : 1,500 (M)	..	..	
Essential oils	..	..	..	germicidal to all in ½ hr. (Cadear and Meunier)
Quinin sulphate	1 : 800 (St)	..	..	
Antipyrin group	1 : 25	..	..	

III. PRACTICAL HINTS FOR THE USE OF ANTISEPTICS.

The following endeavors to give some practical hints of the subject under discussion. The choice of the disinfectant must be largely determined by the objects to be disinfected. These can be roughly classified into:

1. Preservation of food.
2. Excreta.
3. Articles of clothing and furniture; instruments; the skin, etc.
4. Rooms.
5. Operative technic and open wounds.
6. Special situations.

In the beginning, it is well to call attention to the value of *heat*, as this will not be further dwelt upon in this purely pharmacologic treatise. Fire is, of course, the very best of germicides. With steam, a half hour or hour of exposure suffices in most cases. Dry heat of 150° C., continued for one hour, is sufficient to kill any known bacteria or their spores. And the efficiency of chemic disinfectants is always increased by using them hot.

1. Preservation of Food.—Since it is only necessary to prevent the excessive development of bacteria for a limited time, quantities of antiseptics too small to have any appreciable effect upon health are sufficient, unless the substances used possess a marked toxicity. What is the effect, however, of the continued and habitual introduction into the body of even comparatively harmless antiseptics such as are commonly used, is a problem not yet answered. Presumably it is not very great, and the main objection to them rests upon the fraud, in permitting inferior goods to be disposed of as a first-class article.

The principal ones are:

Salicylic Acid.
Boric Acid and Borax.
Sulphite of Lime.

Formaldehyd has recently been introduced for this purpose. On account of the specific irritation of mucous membranes which it causes, it cannot be too strongly condemned.

Creosote and smoke, salt, saltpeter, and sugar are used for preserving food, and are almost or quite free from objectionable features.

2. Excreta and Sputa.—Here must be distinguished between the sterilization of excreta coming from patients afflicted with contagious disease, and the disinfection of ordinary privy vaults. In the latter, cheapness of the disinfectant is a great desideratum, and when only the *excretions of healthy individuals* are to be considered, a deodorant action is sufficient.

Sulphate of iron meets these two indications. Being a metallic salt, it does not penetrate at all readily, and must consequently be frequently applied. It acts by combining with the NH_3 and SH_2.

Where it is necessary to have good penetration, quicklime deserves the preference. It is made into a paste with water. Crude carbolic acid is cheap and efficient if its smell is not too great a drawback. The latter precludes its use for the disinfection of vessels and rooms. Naphthalin is well suited to urinals, since it is so sparingly soluble and very cheap. (Also used to kill moths and other insects.)

For the sick-room, everything considered, chlorinated lime deserves preference. About 6 ozs. of this are taken to a gallon of water, and a quart of this used with each discharge and allowed to stand an hour. Sputa and similar discharges are best received in paper cups or napkins, and burned.

3. For the disinfection of the *hands*, *walls of rooms*, *articles not injured by wet*, etc., mercuric chlorid (1 : 1000) is almost universally applicable. Its only drawback lies in its toxicity. Where this is a serious objection it may be replaced by phenol (2 : 100) or formaldehyd (4% absolute = 10% commercial). These may also be used for *instruments* the metal of which is injured by mercury. Another popular method is to boil the instrument in 1% Na_2CO_3 for half an hour. For *glassware*, dry heat of about 150° C., continued for an hour, deserves preference. The *bedclothing* and *dresses* of patient and nurse should be sterilized by steam, or at least by prolonged boiling. *Wool*, which will not bear damp, can only be satisfactorily sterilized in special apparatus by dry heat of 110° C., or by formaldehyd gas.

4. **Rooms.**—The sponging of rooms and furniture with antiseptic solutions is never sufficient for their sterilization; for there are always many crevices which would escape in such treatment. Some method of fumigation is necessary, and the choice rests mainly between SO_2 and formaldehyd. SO_2 destroys bacteria, but not spores; it is also objectionable since it causes bleaching of all organic dyes. It is generated by burning 3 lbs. of sulphur for each 1000 cubic feet of space. To avoid danger of fire, the sulphur is placed in tin pans raised from the floor by bricks. Its action is materially greater when the air is saturated with moisture.

Formaldehyd is much more efficient, and its only drawback is the cost of the apparatus needed to secure the best results. It is made by burning methyl (wood) alcohol in a special lamp. Whilst formaldehyd is very volatile, it decomposes quite largely if it is attempted to vaporize its solution by heat, and much is lost. However, 150 c.c. of the commercial 40% solution, when vaporized, will disinfect a room of 1000 cubic feet in ten hours. Or a number of sheets saturated with the solution may be suspended in the room.

With all fumigation the room is best kept closed overnight, then thoroughly aired, and then sponged, first with an antiseptic solution, then with water. The wall-paper in particular should be thoroughly cleaned. Where possible, a coat of whitewash should be applied, since this constitutes an efficient germicide.

5. In **operative technic** for open wounds the objects are to avoid local irritant action and general poisoning from absorption, and, if the wound is infected, to obtain the greatest penetration. When the wound is not infected, asepsis rather than antisepsis should be the aim. When the latter is required, preference should be given to carbolic acid (2 : 100) for penetration, and to $HgCl_2$ for local action (1 : 5000 to 2000). Both, it must be remembered, are irritant and capable of absorption. The two can well be used in combination. The tendency of $HgCl_2$ to form insoluble combinations with the constituents of the tissues can be greatly lessened and the keeping qualities improved by the addition of HCl, tartaric acid, NaCl, or NH_4Cl, in amount about equal to the $HgCl_2$. The cresols are rather less poisonous than carbolic acid, but possess no other advantage. H_2O_2 solution is also useful for this purpose. The foam which arises when it comes into contact with decomposing matter supports its action mechanically by dislodging fixed particles of bacteria, dirt, etc.

The local irritant effects are by no means always objectionable; thus, carbolic acid is sometimes used for its caustic action. On account of the anesthesia which it induces, it is very much less painful than other acids; but it is also less efficient. It is sometimes injected in strong solution into cysts to cause adhesive inflammation. Salicylic acid also has a decided caustic action, which determines its use in hyperidrosis, and for softening corns.

The irritation is an objection not only at the place of application, but also at the seat of excretion,—*i. e.*, kidneys,—and nephritis constitutes a contraindication to the use of absorbable antiseptics.

The endeavor to prevent symptoms of general poisoning when a purely local effect is required has led to the use of the insoluble antiseptics as **dusting-powders.** Many of these are also useful in promoting healing by their irritant action; on account of their slight solubility this is always mild and kept within physiologic limits.

A mild irritant action of this kind stimulates cell division and, consequently, healing.

Such products are:

Iodoform, which is not at all germicidal for pure cultures, but appears to be decomposed by living tissues or organ extracts, and by ordinary bacterial cultures, with the liberation of iodin.

When used over large surfaces, or by injection, iodoform has repeatedly given rise to toxic symptoms, consisting in lassitude and somnolence, hallucinations and convulsions, death through general paralysis of the central nervous system. Chronic poisoning shows fatty degenerations in heart, liver, and kidneys. Sodium bicarbonate is stated to be antidotal.

⁂ *Iodoformum* (U.S.P, B.P.).—*Iodoform*.—CHI_3. Made by the reaction of alcohol, iodin, and pot bicarbonate. Yellow crystals of a characteristic odor. Very slightly soluble in water, soluble in 52 parts of alcohol, freely in ether. Contains 90 to 96% of iodin. *Dose:* 0.05 to 0.2 Gm. (1 to 3 grs.).

Unguentum Iodoformi (U.S.P., B.P.) contains 10%.

Suppositoria Iodoformi (B.P.) each contain 0.2 Gm. (3 grs.).

On account of its pronounced odor, recourse has been had to inodorous iodin compounds, some of the best of these having been patented; as

Aristol (dithymol diiodid) and *Iodol* (tetraiodopyrrol); *Nosophen*, *Eudoxin*, and *Antinosin* (tetra-iod-phenol-phthalein and its compounds); *Eigon*, an iodin-albumin compound.

Other antiseptic dusting-powders are:

Of the *aromatic bodies*, principally salol, thymol, naphthol, and acetanilid.

Of *metallic compounds*, mainly the insoluble salts of bismuth; but these may be partly absorbed after continued use and lead to poisoning. The subgallate is the least subject to this.

Boracic acid may also be used as dusting-powder.

6. Antisepsis in Special Situations.—Aside from operative wounds, antiseptic action is often required in various parts of the body, and their use in each region presents special features.

We shall consider:

(*a*) Antisepsis in tissues.
(*b*) Antisepsis in tuberculosis.
(*c*) Skin.
(*d*) Gargles.
(*e*) Intestinal antisepsis.
(*f*) Urinary tract.

(**a**) **Antisepsis in Tissues after Absorption.**—This is as yet only a dream of the future. The only example which we possess of such an action is salicylic acid in acute articular rheumatism. This drug is of very little value in chronic rheumatism or in gout. Benzoic acid has a similar but much weaker action. All other antiseptics kill the animal when present in the tissues in doses much smaller than are necessary to affect the bacteria. But the above-mentioned action of salicylic acid has encouraged the belief that antiseptics may be found which act so specifically on certain micro-organisms as to make them serviceable in this connection. Although this search has so far been unsuccessful, this need not discourage further effort.

(b) The general disease against which antiseptics have been most persistently tried is pulmonary **tuberculosis.** But here also main reliance has been placed upon a local action, from the supposition that some of the aromatic bodies are *excreted through the lungs*. This is indeed the case with tar, creosote, turpentine (terebene), ichthyol, iodoform, benzosol, eucalyptol and other volatile oils. (Ichthyol—1 to 2 Gm. three times a day—is less nauseating than creosote.) But the amount so excreted seems to be too small—at least the sputa of patients thus treated are scarcely less virulent. Nevertheless, these bodies (especially creosol and guaiacol (carbonate)) do seem to exert some favorable influence ; but they do so probably by influencing the nutrition through a mild intestinal antisepsis and stimulation, and also by acting on the bronchitis. They are especially useful in acute infections of the respiratory organs.

Not much greater success has followed the attempt to introduce these antiseptics into the lungs *via* the respiratory passages, in the form of *sprays and inhalations*. The fault lies in the fact that they do not reach the disease foci in this manner, but remain in the upper air-passages. Nor could they readily penetrate the caseous matter, even if they were brought into the alveoli. They are in consequence useful in bronchitis and bronchial pneumonia, but not in tuberculosis.

Great claims have been put forward for the hypodermic and intravenous injection of balsam of Peru and its main constituent, *cinnamic acid*, and its sodium salt, *Hetol*. No marked germicidal quality is claimed for them, but the causation of a *specific inflammation* of the diseased areas with consequent cicatrization. Most observers pronounce themselves unfavorably. Others concede it in "walking cases," but urge the great inconvenience against the treatment: Intravenous injections must be given daily for one and one-half years. The main reliance is still placed on climate and forced feeding.

When tuberculosis is located in more accessible situations—joints, skin, etc.—the outlook is more promising. *Peruvian balsam* appears to be markedly beneficent here also. *Iodoform* has been much used, either as powder or as a suspension (iodoform 10, alcohol and glycerin āā 45).

Thiosinamin, a derivative of oil of mustard, has recently been introduced against lupus. It is given as hypodermic injection of a 15 to 20% alcoholic solution.

To pass now from diseases to the different surfaces of the body which are accessible to local asepsis:

(c) **The Skin.**—Germicides may be useful in this situation in aiding the healing of *sores and ulcers*, or to effect the cure of *more diffuse* skin diseases depending upon the presence of bacteria or other parasites. In either case, a *mild stimulant action* seems to be quite as essential in determining the success of the remedy as the germicidal action. On the other hand, the irritant action must not be too strong. To prevent the maceration of the epidermis, the drugs must be used either as powder or in the form of *ointments.* The latter render the drug capable of absorption, and this prevents the use of any very toxic substance.

The following are the most employed:

Carbolic acid, 5% ointment.

Ichthyol, 10 to 50% ointment. This exerts a peculiarly beneficent irritant action, which also leads to the absorption of inflammatory swellings, etc.

Tar, 10 to 100%.

Resorcin, 5 to 20%. Same action as phenol and no advantage.

Naphtalin and naphtol, 5 to 10% ointment.

Sulphur, 10%.

Pyrogallol (5 to 20%), mainly as irritant, but too dangerous if absorbed, and best replaced by chrysarobin.

The metallic salts and oxids which come under this heading will be considered under astringents (Chap. XXVIII, A).

(d) **Gargles.**—Passing from the skin to the mucous membranes, that of the *mouth* is the most frequently diseased and the most easy of access. Antiseptics are employed here mainly in the form of gargles. They are useful not only when infection has taken place, but also as prophylactics—*e. g.*, to prevent secondary infections, as in scarlatina.

For *gargles* it is well to avoid poisonous drugs, since some of the solution is very frequently swallowed. This constitutes the principal objection to carbolic acid, which is sometimes used in strength of 1%. More insoluble drugs, such as thymol, are better adapted. The essential oils (mentha piperita) are also useful, especially in combinations, since they also act as flavors, a not unimportant item for solutions that are to be used in the mouth. Eucalyptol is preferred by many, although it does not appear to possess any specific advantage. Boric acid is also useful. So is H_2O_2. When an astringent action is also desired, recourse is had to such harmless astringent salts as alum, potassium chlorate, or iron chlorid. The latter, it must be remembered, tends to injure the teeth. The astringent action is also useful, here as elsewhere, in lessening the absorption of the antiseptic, and such combinations of antiseptics with astringents are warmly recommended.

Similar solutions may be used for spraying the throat or for irrigation of the nose. They are used in about the same strength as eye-waters. (See Chap. XXIX.)

(e) The remainder of the alimentary canal is also to some extent subject to the action of antiseptics, although there are some practical difficulties. The possibility of **intestinal antisepsis** has been much discussed, but it has now been proved that *complete asepsis is impossible* in this situation.

This is easily comprehended if one stops to consider the large number of bacteria present; the large mass of material in the intestine, tending to weaken the antiseptic and to prevent its access; the ready absorption and consequent danger of general poisoning; the sensitiveness of the intestinal canal to irritating agencies; the fact that ferment action is diminished by all antiseptics, etc.

The importance of saprophytic bacteria in the process of digestion, on which much stress was formerly placed, has now been disproved.

Although a complete intestinal asepsis is an impossibility, a relative asepsis, a limitation of an abnormally increased bacterial action, is not so. This can be clearly shown by a diminution of the indoxyl and combined sulphates of the urine under appropriate treatment. Calomel may cause their entire disappearance.

These furnish a very good index of bacterial action in the intestine, and are increased or diminished with this; for instance, the administration of alkalies, by neutralizing the acid of the gastric juice, increases the amount of indoxyl in the urine. An increase is sometimes seen in the absence of any digestive disturbance.

The bacteria in the lumen of the intestine will be much more readily acted upon than those which have already obtained a nidus in the intestinal walls, and antiseptic measures will be of greatest benefit in the former condition.

The removal of the contents of the intestines is, of course, one of the most efficient methods, for it carries with it at once numberless bacteria and the material on which they have been nourishing. *Calomel* is the best physic for this purpose, since the slight amount of bichlorid formed from it tends to check the remaining bacteria. The *bichlorid of mercury* is also used in doses of $\frac{1}{2000}$ grain (0.035 mg.). For antiseptics, more strictly speaking, the preference is given to those which are *insoluble*. We may enumerate naphtalin, naphtol, the cresols and guaiacol, thymol, camphor, salol, etc. *Salol* is decomposed into carbolic and salicylic acid. It is only slightly acted upon in the *stomach*, and is used as coating for *pills* which are not to act in stomach. It has been suggested as a test for the length of time during which *food* remains in the stomach, by noting how much time elapses before the salicylic acid test is given by the urine. It is only of limited value, since the time varies greatly in normal individuals.

Most intestinal antiseptics act also as anthelmintics. (See Chap. XXX, F.)

The restraining action of the antiseptics on the digestive ferments is also of some importance in determining their value as intestinal antiseptics and against gastric fermentation.

The following table gives some idea of the comparative restraining influence on the ferments in test-tube experiments:

Least restraining action:

BACTERIA.	YEAST.	PTYALIN.	PEPSIN.	TRYPSIN.
Alum, alcohol, carbolic, benzoic.	½ sat'd salicylic acid. 1% formalin. 5% alcohol.	½% carbolic acid. 1% formalin.	½ sat'd boric acid. 2½% alum.	½% quinin. ½ sat'd benzoic or boric. 5% alcohol. 1 : 10000 $HgCl_2$.
Salicylic.	½% quinin. ½ sat'd salol. ½ sat'd boric acid.	½% quinin. ½ sat'd salicylic acid. 2½% alum. 5% alcohol.	½ sat'd salicylic acid. ½ sat'd salol. 5% alcohol. 1 : 10000 $HgCl_2$.	½ sat'd salicylic. ½ sat'd salol.
Formaldehyd.	½% carbolic acid.	½ sat'd benzoic or boric acid or salol.	½% quinin. ½% carbolic. ½ sat'd benzoic. 1% formalin.	
$HgCl_2$.	1 : 10000 $HgCl_2$.	1 : 10000 $HgCl_2$.		1% formalin.

Most restraining action:

This table cannot, of course, be applied directly to the processes in the intestinal canal; absorption, precipitation, toxicity, etc., also play important parts. However, other things being equal, a substance with the maximum toxicity to the putrefactive organisms and the minimum action on the ferment would be the most desirable. For instance, boric acid would be preferable to salicylic acid against gastric fermentation; mercuric chlorid (or calomel) against bacterial action in the intestine, etc.

(f) Urinary Antiseptics.—The *urinary passages* may be treated by antiseptics in *two ways:* either from the urethra or from the circulation. We shall discuss only the latter in this place. For the urethral antiseptics see Chapter XXVIII. The antiseptics are for the most part excreted in concentrated solution by the kidneys. This constitutes on the one hand a drawback, since it is apt to set up a *nephritis;* but, on the other, it allows us to exhibit *germicidal drugs* in situations not otherwise accessible. In the first place, anything which tends to maintain or to increase the *acid reaction* of the urine will be antiseptic. This is accomplished by mineral acids.

Urotropin is a compound formed by the action of ammonia on formaldehyd. It is partly excreted unchanged, partly as formaldehyd. This excretion begins in a short time, but may last several days. It is claimed that it does not injure the kidneys, and that it may be used in nephritis. It renders the urine aseptic. It is given in the *dose* of 2 Gm. (30 grs.), dissolved in water, after meals.

The others all belong to the aromatic group. The most efficient are: Sodium benzoate and salicylate; salol; balsam of copaiba, oil of cubebs, sandal-wood, etc. (see Chap. XXIX, A). These *resins* are excreted in the urine, and are precipitated by nitric acid. This precipitate must not be confused with albumin.

Uva ursi (also *chimaphila*) contains a glucosid, arbutin, which is ordinarily excreted unchanged, but is split when it comes into contact with a catarrhal mucous membrane, with the production of hydrochinon, an efficient antiseptic.

Uva Ursi (U.S.P., B.P.).—*Bearberry.*—The leaves of *Arctostaphylos Uva-ursi*, Ericaceæ. Northern hemisphere. Also contains considerable tannic acid.

Preparations:

⁂ *Infusum Uvæ Ursi* (B.P.).—5%. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Extractum Uvæ Ursi Fluidum (U.S.P.).—Made with two-fifths alcohol and three-tenths glycerin. *Dose:* 1.0 to 4.0 c.c. (¼ to 1 drachm).

Chimaphila (U.S.P.).—*Pipsissewa; Prince's Pine.*—The leaves of *Chimaphila umbellata*, Ericaceæ. North America. Also contains tannic acid.

Extractum Chimaphilæ Fluidum (U.S.P.).—One-half alcohol. *Dose:* 2.0 to 8.0 c.c. (½ to 2 drachms).

IV. MATERIA MEDICA OF COAL-TAR DISINFECTANTS

⁂ **Acidum Carbolicum** (U.S.P., B.P.) (*Cristallisatum*).—*Carbolic Acid.—Phenol.* C_6H_5OH.

⁂ *Acidum Carbolicum Liquefactum* (B.P.).—Liquefied Carbolic Acid: made by adding 5% to 10% of water to the melted phenol.

The most important preparations are marked ⁂.

Acidum Carbolicum Crudum (U.S.P.).—Crude Carbolic Acid.

Preparation: The coal-tar separated in the process of purifying illuminating gas is subjected to fractional distillation. The portion distilling between 140° and 220° C. is used for Carbolic Acid; it is treated with 10% NaOH, which dissolves the carbolic acid in the form of a sodium carbolate, whilst the impurities remain insoluble. The carbolic acid is then precipitated from its solution by HCl, and washed. This product still contains other substances (especially cresols), and has a reddish color and a very disagreeable odor. It constitutes the "Crude Carbolic Acid." This furnishes the pure by repeated fractional distillation.

Phenol may also be prepared synthetically from benzol.

The *liquefied carbolic acid* is made by melting the crystals and adding the water.

Properties: Carbolic acid, especially when liquefied, acquires a reddish color, probably due to traces of metallic impurities from the distillation vessels. It can be freed from this by redistillation from glass-apparatus, but the color is really of no importance.

Pure carbolic acid melts at 42° C. It is soluble at 15° C. in 15 parts of water, freely soluble in Glycerin, Alcohol, Ether, oils, etc. Glycerin is the most useful solvent, and aqueous solutions of any strength may be made by adding a sufficient quantity of glycerin.

The crude acid is much less soluble than the pure.

Carbolic acid is but rarely used internally, in *dose* of 0.1 Gm., largely diluted, as antipyretic and intestinal disinfectant. It is not well adapted for either purpose. Its principal use is as disinfectant.

For *disinfecting* instruments or hands, the saturated aqueous solution (containing about 5%) is used; for washing wounds, the 3%; for gargles, lotions, and injections, 1%.

Carbolic acid acts scarcely at all antiseptically when in oily solution. But carbolated oil and ointment are useful local anesthetics, dermal irritants, and promote healing. An ointment made from crude carbolic acid is still more effective.

The crude acid is mainly employed as a cheap and efficient disinfectant; the crystallized acid is sometimes employed as a caustic, especially in dental practice.

Preparations:

Glyceritum Acidi Carbolici (U.S.P.) [*Glycerinum Acidi Carbol.*, B.P.].—20%. Useful for making strong solutions.

⁂ *Unguentum Acidi Carbolici* (U.S.P., 5%) [B.P., 4%].—Crude acid may be substituted for the pure.

Suppositoria Acidi Carbolici (B.P.) (against pruritus).—1 grain.

* *Oleum Carbolisatum.*—5%.

Trochisci Acidi Carbolici (B.P.).—Each 1 grain.

The **Sulphocarbolates** are neither as toxic nor as irritant as carbolic acid. However, they have also lost much of its antiseptic effect. The sodium salt is sometimes given to control intestinal fermentation, but would seem to be surpassed by other intestinal antiseptics. The zinc salt may replace the zinc sulphate as astringent.

Sodii Sulphocarbolas (U.S.P., B.P.).—$NaSO_3.C_6H_4(OH) + 2H_2O$. Soluble in 4.8 water, 132 alcohol. *Dose:* 0.3 to 2.0 Gm. (5 to 30 grs.).

⁂ *Zinci Sulphocarbolas* (B.P.).—$Zn(C_6H_5SO_4)_2 + H_2O$. Freely soluble in water. May be used in solutions somewhat stronger than the sulphate.

⁂ *Creosotum* (U.S.P., B.P.), *Creosote.*—A mixture of phenols, chiefly guaiacol and creosol, obtained during the distillation of wood tar, preferably from the beech (*Fagus sylvatica*, Cupuliferæ; temperate zone). Solubility:

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* Not official.

The most important preparations are marked ⁂.

Soluble in 150 parts water, forming rather turbid solution. Freely in alcohol. *Dose:* 0.03 to 0.12 c.c. (½ to 2 minims), preferably in capsules, on full stomach. May be gradually raised to 6 drops if it is well borne.

Preparations:

Aqua Creosoti (U.S.P.).—A 1% solution in water. *Dose:* 4 to 15 c.c. (1 to 4 drachms).

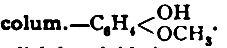
Mistura Creosoti (B.P.).—A 0.2% flavored watery solution. *Dose:* as the water.

Unguentum Creosoti (B.P.).—10%.

The irritant properties of creosote and the gastric derangement produced by these, are important objections to its use in diseases like phthisis, in which a good digestion is perhaps of equal importance to pulmonary antisepsis. In the endeavor to obviate this, a number of preparations have been introduced. Perhaps none of these are an unqualified success, the least irritant being *guaiacol carbonate* (see below).

* *Creosol.*—A combination of 60% creosote with tannin. The creosote is liberated only in the intestine. A hygroscopic powder, readily soluble in water or alcohol. *Dose:* 1 to 9 Gm.

* *Creosotal.*—A creosote carbonate. Thick oil, insoluble in water. *Dose:* 3 to 15 minims.

⁂ **Guaiacolum.**— $C_6H_4<{OH \atop OCH_3}$. This constitutes 60 to 90% of creosote. A liquid, very slightly soluble in water, freely in alcohol. *Dose:* 0.12 to 0.6 c.c. (2 to 10 minims).

Ten to fifteen drops of the saturated alcoholic solution, rubbed for ten to fifteen minutes into the clean and dry skin of the abdomen, act as antipyretic. This action is not seen when the drug is taken by mouth, perhaps because it is not absorbed sufficiently.

⁂ *Guaiacoli Carbonas* (Duotal).—A white powder, insoluble in water. *Dose:* 0.3 to 2.0 Gm. (5 to 30 grs.).

⁂ **Cresols.**— $C_6H_4<{OCH_3 \atop OH}$. Three isomers exist in creosote. They are at once more antiseptic and less toxic than phenol. They are insoluble in water, and are brought into solution by soap (Lysol, Creolin, etc.) or by alkalies (Solveol, Solutol, etc.), and Tricresol (preparation not known; soluble to 2½% in water). They are used in 1% to 2% solution, or in 5% to 10% ointment.

Pix Liquida (U.S.P., B.P.) [*Pix Carbonis Præparata*, B P.].—*Pine Tar.*—An aromatic oleoresin obtained by the destructive distillation of pine woods, particularly that of *Pinus palustris*, Coniferæ, United States. *Dose:* 1 to 4 Gm. (¼ to 1 drachm). Soluble in alcohol or oils; only partly in water Tar consists of a mixture of resinous and volatile principles. When it is subjected to redistillation, it can be separated into a fixed portion,—pitch,—consisting mainly of rosin; and a volatile portion which separates into *Oil of Tar* (*Oleum Picis Liquidæ*, U.S.P.) and pyroligneous (crude acetic) acid. The oil of tar consists of various coal-tar derivatives, mainly Cresols, Guaiacol, Phenol, Xylol, Toluol, and Pyrocatechin. It also contains methyl alcohol and acetone.

Tar is used *externally* as antiseptic, parasiticide, and counterirritant, in the form of:

Unguentum Picis Liquidæ (U.S.P., B.P.).—50%.

Internally, it is used in bronchitis, like creosote, and as an expectorant, most usefully as:

⁂ *Syrupus Picis Liquidæ* (U.S.P.).—*Dose:* 4 to 15 c.c. (1 to 4 drachms).
* *Vinum Picis*, N.F.

Oleum Cadinum (U.S.P., B.P.) (*Oleum Juniperi Empyreumaticum*).—

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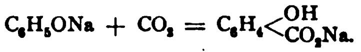
* Not official.
The most important preparations are marked ⁂.

Oil of Cade.—The tar obtained from *Juniperus oxycedrus*, Coniferæ, Mediterranean. Used *externally* like tar, having a less unpleasant odor.

Acidum Salicylicum (U.S.P., B.P.).—*Salicylic Acid.* $HC_7H_5O_3$.

Preparation: (*a*) Synthetically, by the action of CO_2 on sodium carbolate, according to the end-reaction:



$$C_6H_5ONa + CO_2 = C_6H_4{<}\begin{matrix}OH\\CO_2Na.\end{matrix}$$

This sodium salicylate is decomposed by HCl.

(*b*) From oil of wintergreen (methyl salicylate) by saponification with an alkali.

Characters: A white, light, crystalline powder or needles of a sweetish taste, producing sneezing when inhaled. Soluble in 450 parts water or 2.5 parts of alcohol.

Uses: Externally as disinfectant in mouth-washes, etc.; for destroying epidermis, etc. (corns); for preserving food substances, ½ to 6 per 1000. Internally it has been replaced by the salicylates.

Unguentum Acidi Salicylici (B.P.).—2%.

⁂ *Sodii Salicylas* (U.S.P., B.P.).—$NaC_7H_5O_3$. Soluble in 0.9 part of water and in 6 parts alcohol. *Dose:* 0.3 to 2.0 Gm. (5 to 30 grs.). Usually 1 Gm. every hour or two, dissolved in abundant water, until relieved. The solutions soon acquire a brown color.

Lithii Salicylas (U.S.P.).—Very soluble in water and alcohol. *Dose:* As the preceding.

Salicinum (U.S.P., B.P.).—A glucosid derived from several species of willow and poplar. *Soluble* in 28 parts of water or 30 of alcohol. *Dose:* 0.3 to 2.0 Gm. (5 to 30 grs.).

Methyl Salicylate ($CH_3 . C_7H_5O_3$) exists in three forms:

- As a synthetic product: *Methyl Salicylas* (U.S.P.).
- As the volatile oil of *Betula lenta: Oleum Betulæ Volatile* (U.S.P.).—*Oil of Sweet Birch.*
- As the volatile oil of *Gaultheria procumbens: Oleum Gaultheriæ* (U.S.P.).—*Oil of Wintergreen.*

The *dose* of these is 0.06 to 0.3 c c. (1 to 5 minims). They are less irritant and disagreeable, but also much less active, than the sodium salicylate.

* *Aspirin*, see page 371.

⁂ *Salol* (U.S.P., B.P.) (*Phenyl Salicylate*).—Made by heating Salicylic acid with Phenol in the presence of Phosphorus Pentachlorid. Almost insoluble in water; soluble in 10 parts of alcohol and in fixed and volatile oils. *Dose:* 0.3 to 1.0 Gm. (5 to 15 grains).

Acidum Benzoicum (U.S.P., B.P.).—*Benzoic Acid.*—$C_6H_5CO_2H$. Prepared by treatment of Toluol ($C_6H_5CH_3$) with Chlorin and heating with water to 150° C.; or, by sublimation of Gum Benzoin. Soluble in 380 parts of water and 2 parts of alcohol. *Dose:* 0.1 to 0 5 Gm. (2 to 8 grs.). Externally, as ointments, 5 to 10%; as wash, 1% (with addition of alcohol).

Trochiscus Acidi Benzoici (B.P.).—Each ½ grain.

Ammonii Benzoas (U.S.P., B.P.).—$NH_4.C_7H_5O_2$. Soluble in 5 parts water or 28 parts of alcohol. *Dose:* 0.3 to 1 Gm. (5 to 15 grains).

⁂ *Sodii Benzoas* (U.S.P., B.P.).—Soluble in 1.8 parts water or 45 parts alcohol. *Dose:* 0.3 to 1 Gm. (5 to 15 grains).

Lithii Benzoas (U.S.P.).—Soluble in 4 parts water or 12 parts alcohol. *Dose:* 0.3 to 1 Gm. (5 to 15 grains).

The balsams are discussed in Chapter XXIX.

Methylene-Blue.—But slightly soluble. *Dose:* 0.12 to 0.5 Gm. (2 to 8 grains). Largely tried in recent years as diuretic and parasiticide, in malaria, neuralgia, sciatica, cystitis.

* Not official.

The most important preparations are marked ⁂.

*_Pyoktanicum Cæruleum_ (Methyl Violet) } Externally, as disinfectant, 1 to
*_Pyoktanicum Aureum_ (Auramin) } 4 : 10,000, or 2% ointment.

*_Acidum Picricum.—Picric Acid.—Trinitrophenol,_ $C_6H_2.(NO_2)_3.OH$. _Preparation:_ Nitration of Phenyl-sulphuric Acid by Nitric Acid. Yellow crystalline powder of very bitter taste, soluble in 90 parts water, more readily in alcohol. The watery solution stains organic substances an intense yellow. Now obsolete in medicine.

Pyrogallol (U.S.P.) (_Pyrogallic Acid_).—$C_6H_3(OH)_3$. Parasiticide, but too dangerous to be useful.

Naphtalin (U. S. P.) and **Naphtol** (U. S. P., B. P.): Almost insoluble. _Dose:_ 0.3 to 1.0 Gm. (5 to 15 grains).

CHAPTER XVIII.

FEVER (HYPERPYREXIA) AND BACTERIAL POISONS.

I. PHENOMENA OF FEVER.

FEVER is a clinical term denoting a group of phenomena to which belongs necessarily an elevation of temperature. A part of the other symptoms result from this hyperpyrexia, and are, therefore, common to all fevers. Another part are independent of this and characteristic of each fever, and are probably due to direct side-actions of the fever-producing agents.

1. Phenomena produced by elevation of temperature as such; _e. g._, when the animal is kept in a very warm atmosphere (or by heat stroke). The _symptoms_ begin with considerable discomfort; the heart and respiration are accelerated; there is muscular weakness; the animal becomes dull and listless, even paralytic; the pulse becomes so rapid as to be uncountable; the pupils dilate; convulsions may occur just before death.

This evidently points to _stimulation and paralysis of the central nervous system._[1]

If the heating is not carried so far as to produce death considerable _after-effects_ make themselves felt, appearing and persisting after the temperature has been restored to normal. These all point to *degeneration* of various organs, showing clinically as various nervous disturbances, emaciation, and marasmus. It is claimed that they have an anatomic foundation in fatty degeneration of the hepatic and renal epithelium, and skeletal and cardia cmuscles, but it is not proved that simple hyperthermia can produce these degenerations.

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[1] Somewhat similar acute symptoms are noted in the _frog_ when placed in water at 36° C. At first the animal becomes very active and swims about rapidly. The respiration is gradually quickened and becomes so dyspneic that the animal fairly snaps for air. The movements become very weak, and there is a tendency for the animal to float perpendicularly. It makes spasmodic efforts to overcome this. A little later it cannot turn when laid on its back, and soon appears entirely paralyzed. When placed in water at 5°, it returns to normal very rapidly.

* Not official.

Common to all **clinical fevers** are a number of symptoms, both acute and after-effects, corresponding in very many respects to the above—viz., cardiac symptoms, rapid heart and respiration ; degeneration of organs. In addition to these are symptoms referring to the blood, metabolism, vasomotor system, and alimentary canal. These do not appear to be so simply related to hyperthermia, although common to all fevers.

A more detailed study of these changes may be expected to throw some light upon the nature of fever and upon the manner of the action of the substances producing it.

2. Phenomena Common to All Fevers.—Heart : The quickening does not occur in those animals in which the vagus is not tonically active (rabbits), and is, therefore, due to *depression of the central vagus influence.* As would be expected from this, diastole is relatively more shortened than systole.

As to the **blood pressure,** the statements are conflicting. It is probable that it is not affected in the same manner in all cases. It will depend partly upon the heart, which must be supposed to react differently in early and late stages, and besides may be influenced differently in the successive stages ; and partly upon the condition of the *vasomotor mechanism.* The latter, again, is quite variable. In certain stages of some fevers there is a marked dilatation of the cutaneous vessels, mainly central in origin, leading to increased heat loss. In other stages this is conspicuously absent.

In addition to this central influence, bacterial poisons produce *specific* vasomotor paralysis ; *e. g.*, cholera in the intestinal vessels, scarlatina in the skin, etc.

Respiration : This is quickened in all fevers. Sometimes it is more shallow, sometimes deeper than normal. The *respiratory exchange* will follow this fairly closely. It is increased in the earlier, diminished in the later, stages. It is at no time the cause of increased heat production, and depends largely upon the amount of muscular movement on the part of the patient. The *respiratory quotient* $\left(\frac{CO_2}{O_2}\right)$ of the fever patient is low, but this is in part accounted for by the increased secretion of CO_2 in the urine; this, in turn, is due to its larger percentage of NH_3.

Nitrogen Metabolism: The nitrogen excretion is always greater than with the normal individual on the same N-income. So much so, that it is sufficient to account for the increased heat production. It varies quantitatively as the latter. The urea, uric acid, P_2O_5, SO_4, and K all partake in this increase; consequently there must be increased metabolism of cellular, as well as of circulating, proteids. This is evidently not caused by the rise in temperature, since it begins before and persists after this rise.

Further, in certain diseases, as tuberculosis, the metabolism is high, but the temperature remains normal; nor do cold baths, quinin, or salicylates—which lower the temperature—affect the metabolism to a proportionate extent It is, however, conceivable that a rise in temperature may of itself cause a small increase of N metabolism, but one would expect this to show mainly in C metabolism, which, as has been stated, is not greatly increased.

If immunity becomes established as the result of toxin injections, the N increase becomes smaller and smaller after each injection. The P_2O_5 of the urine is finally even *diminished* on toxin injection.

The quantity of **urine** is affected only secondarily through the circulation and through degeneration of the cells. The NaCl is diminished on account of the lessened amount of food. Its molecular concentration is kept near normal by an increased content of nitrogenous molecules. The kidney cells, as well as those of the other glands and muscles, exhibit a cloudy swelling, perhaps a transitory stage to degeneration.

It is perhaps in consequence of this degeneration that the *digestive secretions* are greatly diminished. This involves the saliva, gastric juice, and bile. In consequence there is anorexia. The *sweat glands* seem to be influenced more largely by the circulatory conditions.

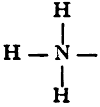
In consequence of the lessened income and greater expenditure, there is a *wasting* of the body fat and proteids. The *alkalinity of the blood* is diminished.

The Central Nervous System: This is affected by a *mixed stimulation and paralysis*. Physical evidences of this are seen in the circulation and respiration. The *intellect* is disordered—at times overactive to delirium; at others, or later in the same case, depressed to narcosis. The *spinal* conclude that the presence of these bacteria in the body generates some poison. It cannot be decided at present whether it should be assumed (1) that the toxin exists preformed as a mother substance and is liberated from the bacteria by their destruction in the body, as is perhaps pyrotoxin; or (2) that the bacteria generate the poison only in combat with the body cells; or (3) that the poison is active only in the nascent state; or (4) that it is formed not by bacteria, but by the body itself in its reaction against the invasion. It is, indeed, very probable that all these are represented in different bacteria.

IV. CHEMISTRY OF BACTERIAL PRODUCTS AND OTHER ANIMAL AND VEGETABLE TOXINS.

This somewhat heterogeneous collection of nitrogenous poisons is usually made to include the following:

1. Ptomains: (Putrefactive alkaloids.) These are "organic bases formed by the action of bacteria on nitrogenous matter."

The majority are oxygen-free, containing C, H, and N, and are, in fact, amins (formed on the type  $H-\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{N}}-H$). In their chemic characters they do not differ essentially from these or from alkaloids. Many do not possess any marked physiologic properties. The rest belong for the most part to the series of atropin to physostigmin, and were briefly treated under meat-poisons. They are most unstable. They are only formed under certain conditions; a certain amount of oxygen is necessary to their formation, yet they are essentially reduction products, and a too liberal amount of oxygen results in the production of non-toxic compounds, often of NH_3, CO_2, and H_2O. They appear early in putrefaction and disappear if this is long continued.

Their main importance arises from their similarity to alkaloids in chemic and physiologic reactions. They may be assumed to be responsible for some legal murders. No one definite feature exists to distinguish them from alkaloids, and the presence of the latter can be affirmed with certainty only when the symptoms and the physiologic and chemic examinations *all* justify the same conclusion.

2. Leucomains: "Basic substances which result from tissue metabolism inside the animal body."

The three chemic classes of which they consist are enumerated on page 187.

The xanthic (alloxuric) class belongs pharmacologically to the caffein group; the nevrinic to the muscarin group.

3. Toxalbumins: Poisons possessing the chemic character of proteids. These include some bacterial poisons, snake venom, and certain vegetable poisons behaving like enzymes.

The serum of all animals contains substances toxic to other species and destroying their blood-corpuscles. These substances are destroyed by heating to beginning turbidity

(55° to 60°), but nothing further is known about their nature.

4. **Toxins:** Bacterial poisons not belonging to any of the above groups.

The last two classes may possibly act after the manner of enzymes. They are largely destroyed by ferments (but not all to the same extent). They are, therefore, comparatively inactive when taken by the mouth. The greater part are also destroyed by moderate heat.

It will be seen that the toxic properties of proteids appear intimately connected with the amin group of their molecule: All the toxic products are nitrogenous, and usually show an amin structure. Amins are chemically very closely related to the very toxic HCN. It has been made out that the combination of HCN with phenol destroys its action; and the theory has been advanced that the living protoplasm consists of such a combination of amids and aromatic bodies, which is broken up by bacteria, etc., resulting in a liberation of these toxic amidic bodies.

V. ANTITOXINS.

One of the most striking characteristics of toxalbumins and toxins is that they are destroyed by specific "antitoxic" substances formed within the body as a result of their own action.

Such an antitoxic power appears to be responsible for the immunity of animals to injections of *serum of the same species.* This antitoxic power appears in all cases to be tied to the serum, and the injection of antitoxic serum immunizes an animal until the antitoxin is destroyed or excreted. This furnishes the basis of serum therapy. The serum must be injected either subcutaneously or intravenously, since the antitoxic power is destroyed by digestion. Immunity of this kind is *quite short,* lasting only as long as the injected antitoxin persists—at most, a few weeks. Very little is known about the *chemic nature* of these antitoxic substances. The only one which has been studied to any extent is that of *diphtheria.* This is either a globulin, identical in most of its characters with the ordinary serum globulin, or, at least, it follows this very closely in its reactions (precipitation by salts, etc.). It is, indeed, not unlikely that "antitoxin" is merely a property developed in these serum globulins, rather than a distinct chemic compound.[1]

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[1] The protective power of blood-serum to certain poisons destroying the erythrocytes (solanin, bee poisons, etc.) appears to be due partly to its phosphates, partly to its proteids. This immunizing action may also be raised by injection of the toxic principles, but this protection is probably of quite a different type from that produced by antitoxins as ordinarily understood.

As little is known about the *manner or seat of their production.*

The diphtheria antitoxin exists in much smaller amounts in organs than in serous fluids, so that it would seem to either arise in the blood itself, or to exist in cells in the form of a mother-substance. Fever neither favors nor delays their formation.

They are *specific,—i. e.,* they protect only against one toxin or organism,[1] and are for the most part produced in reactions of the body against that organism, although they sometimes exist to a small extent in the normal animal.

The normal resistance of animals does not, however, usually depend upon antitoxins, but on another class of substances. Nor can it be said that the immunity is proportional to the amount of antitoxin formed in the blood. Very often an animal may yield a serum very rich in antitoxin, and yet succumb to the disease, and vice versa.

When produced as the result of injection of the toxic substance, the immunity is much more lasting than when produced by the injection of antitoxin. This may perhaps be explained by assuming that they are produced inside the cells, and thus are slower in reaching the circulation and in being destroyed.

Ehrlich has advanced a number of brilliant *hypotheses to account for the phenomena of antitoxic action.* However tempting these may appear, however useful they are as working theories, one must not forget that they rest entirely upon speculative grounds. He supposes the toxins to act only upon a certain part, a "side chain," of the cell complex, destroying this without ordinarily destroying the cell itself. The latter is then able to reproduce the destroyed part. Through this constant exercise in the formation of the side chain, the cells arrive at a condition where they form it in excess, and this excess enters into the serum and imparts to it its antitoxic powers.

From the fact that certain cultures of bacteria are stronger in toxic power, others in producing antitoxin, he assumes that a toxin molecule itself is constituted of two groups, having these actions respectively.

The antitoxins proper, those which have thus far been considered, act by *destroying the toxin.* Whether they do so directly,—*i. e.,* act chemically,—or whether they act physiologically by increasing the destroying power of the body cells, cannot be at present decided. The bulk of the evidence is in favor of a chemic action. They have no direct effect upon bacteria. Indirectly, however, they eventually lead to the destruction of the micro-organisms; for, when the weapons of bacteria are destroyed, the bacteria themselves soon fall prey to the phagocytal and germicidal mechanisms of the body.

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[1] This does not hold true absolutely: an antitoxin may be to some extent effective against other toxins than those of the disease which has given rise to it.

Besides the antitoxic properties, the serum and cells also possess *direct germicidal powers*. The latter are quite distinct from the former. Heating the serum to 55°, *e. g.*, will destroy the latter, but not the former. There is a general germicidal power possessed by all animals, and effective to some extent against all bacteria. There is also a specific germicidal power developed like the antitoxin in the organs struggling against the special bacteria. This exists, *e. g.*, in typhoid, cholera, and streptococcus infection. The agglutinating power of typhoid serum for typhoid bacteria, an instance of germicidal action, is made use of in diagnosis.

This much seems certain: that the immunizing substance is developed as a result of the successful struggle of the animal against the bacteria or their toxins.

Immunity may be obtained:

(*a*) By one attack of the disease.

(*b*) By inoculation of the attenuated cultures or by very small quantities of the virulent cultures.

(*c*) By inoculation of sterilized cultures (*i. e.*, toxins in sublethal doses).

(*d*) Therapeutically the result is usually more satisfactory and less dangerous, but less lasting, if the *antitoxic serum* is injected. These injections are usually made into regions of loose cellular tissue—the space between the scapulæ; the inner aspect of the thighs; into the gluteal muscles. If aseptic, they present no danger or deleterious effect in the quantity in which they are employed, beyond occasional exanthemata. The following are in use at present (Table XV, pp. 400 and 401):

TABLE XV.—ANTITOXINS AND PROTECTIVE SERUMS, CULTURES, AND VIRUS.[1]

DISEASES.	BIOLOGIC THERAPEUTICS.			METHOD OF EMPLOYMENT. (By Hypodermic Injection unless otherwise stated.)		RESULTS.		DURATION OF ARTIFICIAL IMMUNITY (APPROXIMATE AVERAGE).
	Antitoxic Serum. (Made by immunizing animals to toxins.)	AntimicrobicSerum (Made by immunizing animals to living cultures.)	Prophylactic Virus.	Prophylactic.	Curative.	Prophylaxis.	Treatment.	
Variola . . .			Vaccine: preparations of the crusts and purulent matter from heifers inoculated with vaccinia.	Dermal introduction upon a scarified surface.		Excellent.	None.	From human scab, forty years; from cow-virus, four to ten years.
Diphtheria . .	Serum of horse immunized to diphtheria toxin.			500 units. (Children 200 units.)	1000 to 3000 units repeated every four to five hours as necessary.	Excellent.	Reduction of death-rate from 30 to 10 per cent. in large hospitals.	Six to twelve weeks.
Tetanus . . .	Serum of horse immunized to tetanus toxin.			10 c.c. of 1 : 500,000 strength.	4 doses of 50 c.c. each.	Good.	Doubtful.	
Snake-bite . .	Serum of horse immunized to cobra venom.				Doses of 10 to 20 c.c., frequently repeated.		Fair success if used early.	
Bubonic plague			Sterilized bouillon culture (Haffkine prophylactic).	1 c.c.		Good.		One month.
	Serum of horse immunized to live virulent cultures of the plague bacillus (Roux-Yersin Serum).			5 to 25 c.c.	50 to 150 c.c. frequently repeated.	Good.	Fair success if used early.	Two weeks.

Pneumococcus	Serum of horse immunized to live cultures of the pneumococcus.				10 to 20 c.c. repeated every four hours.		Doubtful.	
Hydrophobia .			Crushed infected spinal cord, attenuated by drying.			Good.	Fair if used early.	
Streptococcus		Serum of horse immunized to streptococcus cultures.		10 c.c.	20 c.c.	Doubtful.		
Pertussis . . .	Human serum.				10 c.c.		Fair.	
Cholera			First 1 c.c. of attenuated culture, then 1 or 2 c.c. of virulent culture (Haffkine).			Good.		
Typhoid . .			Sterilized bouillon culture.	1 c.c.		Fair.		

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[1] I am indebted to Prof. Jos. McFarland for much valuable aid in the preparation of this table.

Kidney: The result is nephritis; at first parenchymatous, later interstitial. It is generally diffuse, and presumably due to the excretion of irritant toxins, since the kidneys are frequently sterile. It may be seen in a number of infections, but is most conspicuous in scarlatina, diphtheria, cholera, typhoid, etc.

Liver: Generally focal; *e. g.*, malaria, typhoid. The epithelium degenerates and the connective tissue proliferates. There is a peculiar affection in yellow fever.

Cardiac and Skeletal Muscles: These are affected by many toxins. The most typical toxin in this respect is that of diphtheria.

The injection of diphtheria toxin causes acute functional depression of the heart. This occurs comparatively late—*i. e.*, when the toxin has already disappeared from the blood; the explanation being that it is then fixed in the cells.

Lymph Glands and Spleen: These show changes of the same type as in the case of the liver. Typhoid toxin stimulates in particular the production of leucocytes and of the endothelium of blood and lymph vessels—probably not that of fibrous tissue.

Peripheral Neuritis: This is seen most frequently in paralysis from diphtheria and scarlet fever. It is most striking in the tropical disease, beriberi, and a very chronic change is seen in leprosy. The muscular pains noted in many acute infections—*e. g.*, influenza—are perhaps neuritic.

Alimentary Canal: This is frequently affected as the portal of entry. Certain organisms, however, seem to possess a predilection for it, such as those of cholera, typhoid, coli communis, and yellow fever.

Respiratory Organs: These are especially subject to the infections by tuberculosis and pneumococcus, although many others may lodge there.

The *joints* are specifically affected in rheumatism and gonococcus infection.

If the inflammatory process is a slow and chronic one, it leads to a more pronounced connective-tissue proliferation rather than a direct tissue necrosis. This is seen in tuberculosis, syphilis, etc.

5. Red Blood-corpuscles.—These are affected either in the way of: (*a*) Laking or destruction. (*b*) Agglutination.

(*a*) *Laking:* This is a phenomenon seen with many protoplasmic poisons; saponins, solanin, etc.; also bile acids,

AsH_3, water, or hypoisotonic solutions of salts, hydrocarbons, heat, etc.

Of the present poisons this property is possessed particularly by animal toxalbumins, as blood-serum of a foreign species (particularly carnivorous for herbivorous animals; most violent in eels' serum). Solution of corpuscles is also a prominent property of bee poison, snake venom, etc.

Agglutination—*i. e.*, the clumping of blood-corpuscles—is shown by ricin and abrin.

Bacteria themselves are also agglutinated more or less specifically by various substances, and especially by serum. This does not seem to be concerned with immunity.

The change in the blood leading to intravascular clotting as produced by certain nucleins, or the diminution of coagulability as produced by albumoses, may also be mentioned under this heading.

6. Central Nervous System.—The effects on the central nervous system are due largely to hyperpyrexia, to the disturbed circulation, to the production of embolism, etc. In addition to this, however, a number of toxins have undoubtedly a direct action on the nerve-centers. This is perhaps most conspicuous in the stimulation of the cord produced by tetanus and hydrophobia. Pertussis is also a spasmodic affection which must be due to a specific irritation.

The *effects on the medullary centers* consist mainly in depression. Diphtheria paralyzes the vasomotor, and then the respiratory, centers; snake venom, the respiratory center first, etc.

The specific effects upon the *hemispheres* cannot be sharply differentiated from those due to hyperpyrexia, but there can be no doubt that certain toxins produce delirium; others, comatose conditions, etc.

The disturbances of the metabolism and of the temperature centers have already been discussed.

7. Lowered Resistance.—While an attack of an infectious disease generally causes some degree of immunity to the same organism, it lowers resistance to other infections, especially for the same organs. Thus, bronchitis makes a patient more liable to pneumonia, etc. Chloral and alcohol also increase the susceptibility to a number of diseases. So does castration, both in males and females.

8. Mechanical Effects.—The bodies of the bacteria, if present in sufficient numbers, will produce mechanically embolisms of various portions of the circulatory system, as of the coronary arteries or of vessels supplying important parts of the central nervous system, and in this way produce death. Anthrax infection is a good example.

VII. PHARMACOLOGY OF SOME SPECIFIC INFECTIONS.

For the sake of illustration, some of the typical intoxications may be entered into somewhat more fully.

The subject of infection by tetanus and cholera is discussed elsewhere (page 167 and Chap. XXVII). Both are toxic processes.

1. **Diphtheria.**—This disease is particularly adapted to the study of toxin-poisoning, since the bacteria remain localized and the general phenomena are almost purely those of the toxin.

The **local phenomena** consist in exudative inflammation and necrosis of tissue. Hyaline thrombi are formed in the vessels, and these may give rise to embolism. Localized degenerations may also occur in distant organs. These may be due to the toxin alone, in which case they are diffuse (cloudy and fatty) and affect particularly glandular epithelium (kidney and liver), muscle (skeletal [?], but particularly cardiac), and lymphadenoid tissue (spleen).

The **systemic action** consists in slowly developing paralysis of the medullary centers (respiratory and vasomotor), and later of the cardiac muscle.

The *functional cardiac changes* consist, in the first place, in quickening and weakening such as is seen in other fevers as a result of the hyperpyrexia. After some days this gives place to a slowing. The latter is *muscular*, for it occurs after atropin. The cause of the delayed action is to be sought in the slow penetration of the toxin. The effect of the toxin on the isolated apex (Porter method) consists in slowing without diminution in force. Repeated diphtheritic intoxication causes *chronic atrophy* of the cardiac muscles, probably due to nervous and vasomotor disturbance, but as yet not well understood. It occurs even when the disease has been stopped by antitoxin.

Little is known as yet of the cause of changes in the *central nervous system*. These may partly be due to hyperpyrexia, partly to embolism, but a large part may be assumed to be caused by the direct action of the toxins on the nervous elements.

Injection of the toxin produces late vasomotor paralysis (which precedes the cardiac paralysis) and depression of the respiratory center. The fall of pressure from the vasomotor paralysis is considered the primary cause of death, if this occurs within forty-eight hours.

The *peripheral nerves* are irritated through localized neurites.

The proportion of urea to the total nitrogen is increased.

The toxin is precipitated by absolute alcohol, ammonium sulphate, or magnesium sulphate. It is non-dialyzable. It is rendered inert at 50° to 60° C.

2. **Scarlatina.**—The **skin affection** begins in the hair follicles, but soon extends as hyperemia to the whole skin. This disappears on pressure and returns very slowly, which favors the theory of *paralysis of the vessels*. This is further confirmed by a hydrops of the skin, which is independent of renal and cardiac affections. Since this is confined to the skin, it is probably *peripheral*. The phenomena—erythema, exfoliation, etc.—are those of dermatitis due to vasomotor paralysis. The dermatitis is synchronous with the fever; but since the severity of the two is very different, and since one acts centrally and the other peripherally, there is some probability of the existence of two different toxins, generated by the same process. There is a general resemblance to drugs producing erythema.

The General Affection: Considering the necessarily increased heat loss from dilatation of the skin vessels, the fever must be due to an *increased heat production*. The greatly quickened pulse speaks for a paralytic process; the small degeneration of the heart muscle would make this appear partly central. But a peripheral toxic effect is shown by the hemolysis. We have here the usual effects of an irritant poison: increased metabolism resulting from destructive processes. Neurites sometimes occur without sepsis, leucocytosis, etc.

Nephritis: This is peculiar from the fact that it comes on after the other processes have subsided, and is independent of their severity. The independence may perhaps be accounted for by a slow excretion of the toxin, which would cause the maximum concentration to come on late. Otherwise one would be forced to assume the presence of a third toxin formed independently from the rest.

To summarize scarlatina toxin: The irritant effects are shown in different ways, possibly due to different substances; at all events, independent of one another.

1. Skin: It paralyzes the blood-vessels peripherally.
2. General: Increased metabolism. Cardiac paralysis. Hemolysis, etc.
3. On its excretion, which is slow, it develops nephritis.

It resembles most closely the cantharidin group.

On account of the vasomotor paralysis, it lowers the resistance to pus organisms.

3. **Typhoid.**—This is a mild toxin process, mainly irritant in its effects.

The *local action* results in solution of tissue, necrosis of vessels, etc. If the process is localized in the intestinal canal, it causes an increase in the secretion of mucus.

At a distance it stimulates the production of leucocytes and of the endothelium of the blood- and lymph-vessels, but probably not that of fibrous tissue. It causes hyperemia of various organs (nose, etc.), fatty degeneration and cloudy swelling of the renal and hepatic epithelium and cardiac muscle. Focal infections are common.

The toxin has a digitalis effect upon the *isolated heart.*

4. **Pus Organisms.**—These cause mainly local necrotic and lytic changes, connected with the actual presence of the bacteria.

If these leave their local situation and invade the body, the result is septicemia; if this gives rise to infected emboli, we have pyemia; if their toxins alone enter the circulation in sufficiently large quantities to produce marked effects, this is called toxemia.

Their systemic effects resemble very closely those of albumoses and other fever-producing agents.

5. **Tuberculosis.**—The bacteria produce *chronic inflammatory changes* due to the slow liberation of a toxin. Their action consists in a toxic effect on protoplasm and a stimulating effect of the fixed connective-tissue cells. There are also general metabolic changes inducing cachexia. The bacteria have no marked predilection for any special organ, beyond the seat of introduction.

Tuberculin (a glycerin extract of the bacteria) contains a peculiar proteid substance which is not destroyed at the temperature of 120° C. This has no effect upon healthy animals, but is very toxic to individuals already infected with tuberculosis, causing inflammatory and pyrogenetic changes.

The reason for this predilection must be sought in the fact that the tuberculin only heightens the normal tuberculosis process and cannot act unless the latter is already present. It is therefore used in diagnosis of obscure cases of tuberculosis. Almost all clinicians are now agreed that it presents no danger. The dose for this purpose is 5 to 10 mg., given hypodermically. It must be remembered that the injection of normal saline alone causes a slight rise of temperature in sensitive individuals. When the tubercular process is far advanced, the tuberculin reaction may fail, since the patient is already saturated with the toxin.

6. **Syphilis.**—The action of the syphilis poison consists apparently of a *general protoplasmic irritation* with a special tendency to cell proliferation.

The *local changes* are purely proliferative and irritant; in part acute (chancre); subacute and exerted on the skin and mucous membranes (secondary syphilides); or slow, similar to those of tuberculosis, with production of gummata, ulceration, etc.

There is also an alteration in the *general metabolism*, as yet but little studied.

7. **Beriberi.**—Opinion differs as to whether this disease is an infective process or is produced by toxins contained in food (fish). The symptoms present several forms, which may all be reduced to degenerative changes in nerve-trunks and consequent trophic disturbances. The main forms are multiple neuritis, anemia, and anasarca. The neuritis is generally an ascending motor paralysis, sensory disturbances also appearing later. Injections of the blood cause, in the cat, effects which correspond to those of cholin.

8. **Anthrax.**—Besides local inflammatory changes, there is a general intoxication, which seems to be due purely to the mechanical obstruction of the capillaries by the bodies of the bacteria themselves. The toxin, if any exists, is very weak.

9. **Albumoses and Peptones.**—The production of *fever* by the injection of these substances has already been studied. Besides this, the intravenous injection of albumose in small doses hastens the *coagulation of the blood*. In larger doses it retards this. This action cannot be obtained by mixing the peptone with blood outside the body, but seems to be due to the stimulation by this albumose of the production of substances favoring or retarding coagulation.

Proteoses also produce a considerable fall of blood pressure, due to *vasomotor paralysis*, especially of the splanchnic area. Whether this is central or peripheral is still under discussion.

It has recently been claimed that albumoses prepared under strict asepsis are without action, and that the commonly observed effects are due to the admixture of ptomains. This statement requires further confirmation.

Other proteid bodies probably have a similar action; also certain proteid derivatives, such as the *protamins*, *histones*, etc.

VIII. PHARMACOLOGY OF ANIMAL VENOMS.

1. Of the animal poisons belonging to this type the most typical are the **snake venoms.**

While the different snake poisons are not exactly alike, they present, on the whole, *two actions* differing quantitatively in different species: First, a local toxic effect on protoplasm, leading to irritation, edema and gangrene, and destruction of blood-corpuscles; second, a general action resembling most closely that of coniin.

The **local effect** commences in a *cellulitis* at the site of the bite. This is accompanied by swelling, and later goes into gangrene.

Very marked changes occur in the *blood.* There is a considerable tendency to extravasation, also thrombosis. The coagulability of the blood is changed in a manner similar to albumoses, and this action is, indeed, most marked if albumoses are present in the venom.

A solution of the red corpuscles and laking of the blood is a very frequent phenomenon even in the intact animal. The hemolytic action is less apparent on the blood of the snake itself and upon that of immunized animals.

Systemic Actions.—These are nervous, mainly central, partly peripheral.

The *central nervous system* is affected in almost the same way as by coniin, but with a more direct paralysis of the respiratory center. There is a period of incubation (in man, of about four hours' duration); the patient then becomes drowsy, and then presents an ascending paralysis of the cord—*i. e.*, in the order of legs, arms, larynx, and tongue. There is also salivation and vomiting. The respiration becomes dyspneic, giving rise to asphyxial convulsions and forming the cause of death. The heart beats for some time after the respiration stops.

This is the picture for cobra venom. The venom of the Indian viper contains albumose, and, like the latter, produces a *fall of blood pressure.*

A paralysis of the vasomotor center is frequent with these poisons, leading to a fall of blood pressure. The latter is in part due to peripheral effects on the heart and on the endings of the splanchnics. In the heart the paralysis involves both ganglia and muscle.

Another analogy to coniin is a *curare action* of these poisons.

Primary *convulsions* are not so conspicuous, but may be present.

A rabbit poisoned by rattlesnake venom exhibited longitudinal rotations among other symptoms, and the autopsy showed chromolytic changes in Purkinje's cells.

Nature of the Active Substances.—These are neither living organisms nor alkaloids. They are destroyed by heat, but withstand drying at low temperature and will then keep indefinitely. They are *proteids*, and belong to all the different classes—albumins, etc.

Their toxic property appears to be mainly an exaggeration of the normal toxicity of serum proteids, which last present qualitatively the same actions.

The cobra venom contains a globulin and a modified albumin, which causes a paralysis of the respiratory center; and serum albumin, which produces the ascending motor paralysis.

The Indian viper (Duboia) contains a globulin and an albumin similar to those of the cobra, and, in addition, an albumose which causes a vasomotor paralysis and a lessening of the coagulability of the blood.

These proteids are destroyed to a slight extent by the liver, but not by the nerve-substance. They are destroyed by ferments, and are therefore harmless when taken by mouth; but if introduced into the alimentary canal below the pancreatic duct, they are absorbed unchanged and exert their typical action.

The snake venoms, and particularly the blood of the snakes, contain specific **immunizing substances** which are more resistant to heat than the toxalbumins. Artificial immunity can also be established in animals by the same methods as are employed against bacterial toxins. The hedgehog is naturally immune, and will survive an amount of poison proportionately thirty or forty times larger than will the guinea-pig. This immunity can be transmitted to the guinea by injection of the hedgehog serum. Snake antitoxins obtained from immunized horses are now on the market, and appear to be fairly successful.

It is possible that the snake charmers enjoy an acquired immunity; but, more often, they cause the serpents to bite into a stick a number of times, in this way exhausting the supply of poison, or else they extract the fangs with the poison-producing glands.

The **treatment** of snake-poisoning consists in ligation of the infected part, expression, excision, cauterization, or irrigation with 1 % $KMnO_4$ solution or with iodin. The general treatment should be stimulation with strychnin in large doses. This has given brilliant success. The popular treatment by large doses of alcohol is largely empirical. Medullary stimulants may also be employed.

The importance of this subject may be appreciated from the fact that in India in 1898, 22,000 people were reported as killed by snake bite.

2. Certain **lizards** (Gila monster) secrete poisons having close resemblance to that of snakes.

3. Certain **poisonous fish** have glands analogous to those of snakes, and the poison from these produces a similar cellulitis. Most instances of fish poisoning are due, however, to the eating of their poisonous meat (see p. 270).

4. The skin glands of the **toad** secrete a poison (phrynin) which is very irritant to the skin and mucous membranes. Applied directly to frogs' hearts, it exerts a digitalis action. This perhaps explains the comparative immunity of toads to digitalis.

5. The skin of the fire **salamander** (salamandra maculata) secretes alkaloidal poisons which have a local irritant and a strychnin action, and if injected, produce death by respiratory paralysis.

6. **Scorpions** contain glands on the abdomen which secrete a poison which may have an action similar to that of the salamander. Artificial immunity may be acquired by the use of gradually increasing doses, and this protects even against the local reaction.

7. **Bees, wasps, hornets, mosquitos,** and **ants** secrete a poison which produces a local irritation. This contains formic acid, but the nature of the active substance, probably toxalbumins, is not known. One of the most efficient antidotes to insect-poisoning is the local injection of a solution of ammonia water.

8. **Spiders** secrete two poisons from separate glands. One has a local irritant action, the other is a toxalbumin and possesses systemic actions. These consist in trembling, fast pulse, cold sweat, nausea, and vomiting. The effect is rarely, if ever, fatal.

IX. TOXINS OF VEGETABLE ORIGIN.

These are not true proteids, but they seem to exist in the plants as proteid-compounds.

The most important is **Ricin,** contained in the castor oil bean. Poisoning from eating these seeds is fairly common in literature, and presents a mortality of about 6%. The ricin is contained in the press cake which remains after the expression of the oil. It is extremely toxic, 0.04 mg. per kilo being fatal for rabbits.

As to its **action**: Taken by mouth, it is at first an *irritant* after the manner of croton oil, causing a rather slow irritation of the intestines. This irritation seems to rest on a local *intravascular coagulation*, leading to the effusion of blood, ulcer formation, etc. This action occurs wherever the poison is applied, but the conjunctiva is particularly subject to it. The intestinal canal is less affected because the irritant part of the poison is destroyed by ferments. Besides this local effect of the poison, it produces death after several days from *central symptoms*, especially when it has been injected hypodermically or into the circulation. The medulla is suddenly affected, showing paralysis of the vasomotor and respiratory centers similar to that produced by snake poisons and some bacterial toxins. Given hypodermically, the ricin is even more toxic than strychnin. It could not be demonstrated chemically.

The **symptoms** in man consist in nausea, vomiting, colic, bloody diarrhea, headache, thirst, hot skin, small frequent pulse, cold sweat, icterus, convulsions, and anemia, and death in convulsions or from exhaustion.

Another similarity to bacterial toxins consists in the acquisition of an **immunity**. This can be established to such a degree by feeding the poison, that the animal may bear 5000 times the normal fatal dose.

Outside the body it acts on the blood of all vertebrates, producing a *conglutination of the red corpuscles*. This does not occur in living animals. It is not affected by immunity to the toxic substance. It is destroyed by ferments, whereas the centrally acting poisons are not. Hence ricin contains two, and perhaps three, different substances: producing extravascular conglomeration; intravascular clotting; and the effect on the central nervous system. But it is very possible that the latter is the indirect consequence of the clotting.

Abrin, a toxalbumin from Jequirity bean, resembles ricin so closely in its action that the difference was only established when it was noticed that immunity against one did not constitute immunity against the other. When the whole beans are swallowed, no toxic effects result, since the shell is so hard that the poison does not dissolve. But if the powder is taken, it produces effects similar to ricin. The action on the eye is much stronger, causing ophthalmitis. This is sometimes utilized therapeutically, but is not justifiable, since it is impossible to control the action.

***Abrus precatorius**.—*Jequirity Bean, Prayer Bean*.—Papilionaceæ; tropics. An infusion may be made by macerating the powder with 50 parts of cold water.

Phallin and Helvella-acid.—These are toxalbumins contained in Helvella esculenta, Amanita phalloides, and other mushrooms.

Their action consists especially in a very marked solvent power on red blood-corpuscles, similar to that produced by saponins, but occurring inside the body. This results in extravasation of blood, dissolution, and a number of similar actions. Some of their effects are also primary. The symptoms show a close analogy to yellow atrophy of the liver. These symptoms appear only after hours, or sometimes after days. They consist in gastro-enteritis, cold sweat, somnolence, headache, delirium, coma, convulsions, cyanosis, fever, hemoglobinuria, and albuminuria or anuria.

These poisons are destroyed by drying, or may be removed by hot water, so that these mushrooms may be eaten with impunity after this treatment.

* Not official.

CHAPTER XIX.

THE SERIES OF HYDROCARBON NARCOTICS.

(ALCOHOL AND CHLOROFORM GROUPS.)

(A) GENERAL.

I. INFLUENCE OF CHEMIC STRUCTURE ON ACTION.

THIS series includes all such hydrocarbon compounds—derivatives of the fatty series C_nH_{2n+2}—in which the hydrocarbon portion is the active part. In order that they may exert their specific pharmacologic action, it is, of course, necessary that they be capable of absorption and distribution in the liquids and tissues of the body. This may be either by direct solution, as in the case of chloral; or, in virtue of their volatility, as with chloroform. Members of the series which are neither soluble nor volatile—such as paraffin—have no action.

The influence of chemic structure upon the action has been more fully studied in this series than in any other. Whilst it cannot be said that this study has brought us any nearer to the explanation of the action, it has, none the less, furnished us with a number of interesting facts which show at least a fairly definite relation between changes in the chemic make-up and pharmacologic action of drugs.

As a first rule, we may say that, other things being equal, the strength of action increases with the length of the chain; the greater the value of n, the stronger will be the action.[1] A limit is soon reached, however, for the drugs become less volatile and less soluble the higher they stand in the series; so that the higher paraffins are entirely insoluble and inactive. The action may be modified by replacing the H of the group by other elements or groups. The compounds so formed all possess the typical action of the hydrocarbon group; but this may be so overshadowed by other actions as to be scarcely appreciable. A good example of this is the introduction of the group NO_2. This acts very much more strongly than the hydrocarbon part of the molecule, and consequently the nitrite action is obtained long before there can be any hydrocarbon action. The same is true if we substitute an aromatic radicle. The introduction of certain other radicles weakens the hydrocarbon action to a very great extent. We may mention especially the acid-forming radicle CO_2H. The introduction of hydrocarbon radicles into an amin molecule destroys their action entirely. The introduction of more than one OH group also weakens or destroys the action. Aldehyds are more active than the corresponding alcohols. The introduction of the halogens, and especially of Cl, often enhances the action, but this is not proportional to the number of Cl molecules introduced. The introduction of O (ethers) also increases the action. The introduction of acids (esters) weakens it.

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[1] The boiling-point and the relative toxicity of the alcohols are given as follows:

	BOILING-POINT.	TOXICITY (BAER).
Methyl, CH_3OH, ...	65.0	0.8
Ethyl, C_2H_5OH, ...	78.5	1.0
Propyl, C_3H_7OH, ...	98.0	2.0
Butyl, C_4H_9OH, ...	107.0	3.0
Amyl, $C_5H_{11}OH$, ...	131.0	4.0

II. SUMMARY OF ACTIONS.

1. A precipitation of proteids, leading to irritation and death of tissues, and hindering the action of ferments and the growth of bacteria.
2. Reflex actions resulting from this irritation.
3. A depressant (narcotic) action upon the central nervous system, exerted primarily upon the higher centers of the brain, and lastly upon the medulla.
4. In the case of alcohol, the capability of oxidation and consequently of acting as a food.

III. DETAILS OF ACTION.

1. The **local action** rests largely on a coagulation of proteids, just as in the case of the aromatic antiseptics.

The cause of this coagulation differs in some respects in the various members. In the case of *alcohol* it rests upon withdrawal of water, and consequently all proteids are affected; *chloroform* has a more marked action upon globulins (especially myosin), and *ether* upon albumins (especially egg-albumen). Many of the other members of the series resemble one or the other of these three.

2. This coagulation of protoplasm causes **irritation and inflammation,**—an increase followed by diminution and finally abolition of function,—which are manifested in various ways on the administration of these substances.

When given in concentrated form, they cause a sensation of burning on the **mucous membranes** with which they come in contact. This is strongest with the aldehyds (*e. g.*, *formaldehyd*, and acrolein, the irritant vapor formed in the overheating of oils). In the *stomach* they give rise to vomiting (especially chloroform). The continued use of concentrated alcoholic liquids brings about chronic gastric catarrh, and consequently impairment of nutrition. In dilute form the changes are much less, and may even be absent. This will be more fully discussed on page 431.

Whilst alcohol is partly burned, much of it remains unchanged, and this holds still more of most of the other members of the series. During their **passage through the body** they cause similar irritations in other organs. These are most marked in the *liver and kidneys*, and result in inflammatory changes, especially interstitial. If the course of the poisoning is slow, as in alcohol, *connective-tissue proliferation and fatty degeneration* are the principal lesions. Chloroform and ether produce inflammation of the kidneys much more quickly than alcohol; a single administration may result in typical acute nephritis with albumin casts, hemoglobin, etc. It is scarcely necessary to assume a special susceptibility of these organs toward the local action of the series, since they are situated respectively at the portal of entry and of exit, where the drugs are, of course, in the most concentrated form.

Smaller doses of alcohol cause *diuresis* through this irritant action.

In addition to their coagulant action, the insoluble and volatile members of the series irritate as molecular foreign bodies, since they penetrate tissues readily by virtue of their volatility, but do not mix with their constituents. On this quality rests their employment as embrocations: they produce a slight but deep irritation. When applied to the **skin,** this results in redness and a sensation of burning, which in the case of some (chloroform) becomes very *painful.* This is followed by local *anesthesia.* Alcohol in greater dilution (25% to 50%) produces an increased cell division when applied to wounds, and an increased secretion of digestive juices and more rapid absorption when taken by the stomach.

When the more volatile members are applied to the skin and allowed to evaporate, this abstracts heat, resulting in a *sensation of coolness,* in place of the burning noticed if they are rubbed in or covered. This abstraction of heat may be carried to actual freezing of the tissues by using the volatile substance in the form of spray—a method made use of for the production of local anesthesia. (See p. 239.) Some also cause stimulation of the *nerves of* **taste and smell**; the bouquet of wines and liquors is due to members of this series—for the most part unknown—and grouped together under the name "*œnanthic ethers.*"

Applied directly to a **muscle or nerve,** they act like any other protoplasmic poison, producing increase and then diminution of function.

When injected near a nerve-trunk, they may cause paralysis due to a circumscribed neuritis—a fact important to bear in mind in making hypodermic injections of alcohol or ether.

The coagulating action also determines the **antiseptic properties** of this series. Their efficiency is much less than that of the aromatic group.

Iodoform owes its action, not to the hydrocarbon part of its molecule, but to the iodin liberated from it.

The hydrocarbons are also very efficient parasiticides.

They are of no great value as *anthelmintics*, since they are too rapidly absorbed and produce too great a local irritation.

3. The **action upon the central nervous system** is *purely depressant*, according to most pharmacologists. It agrees with morphin in affecting primarily the higher psychic functions, but differs from it in lowering, instead of heightening, the reflexes.

Four stages may be distinguished in this nervous action :

1. The so-called "*stimulant*" *stage*, when the activity of certain centers appears increased.
2. The *narcotic stage*, in which a marked lowering of the psychic functions and a disturbance of the "balance of the brain" become apparent.
3. The *anesthetic stage*, with loss of motion, of consciousness, of sensibility to pain, and of some reflexes.
4. The *paralytic stage*, with total abolition of the cerebral, spinal, and lastly of the medullary centers, the latter causing death.

This description applies to all the hydrocarbons which may be classed in this series. But great differences exist in the readiness with which one stage passes into the other. These differences are merely quantitative. Alcohol, ether, and chloroform, for instance, form a regular series in this respect. But this difference is an extremely important one practically, so that it will be better, in so far as the action on the central nervous system and the therapeutic uses are concerned, to subdivide the subject into three groups, placing alcohol in one, the general anesthetics in the next, and the hypnotics of the hydrocarbon series in the third.

(B) THE ALCOHOL GROUP.

I. THE STIMULANT OR EXCITEMENT STAGE

is observed in most cases after taking "moderate" doses of alcohol—a quantity not easily expressed in cubic centimeters. The phenomena are only too well known. They are, at first view, typical of stimulation. There is an increase in the rate of the *respiration* and of the *heart;* the *blood pressure* rises. The *skin* is reddened, with a grateful sensation of warmth and comfort. There is an increased *vivacity* of motion, action, and speech, which latter may acquire a stamp of brilliancy, even of inspiration. The *subjective condition* of the individual also undergoes a peculiar change.

Shyness, if it ordinarily exists, is replaced by self-confidence. The person under the influence of alcohol feels an unlimited confidence in his own powers and accomplishments, both intellectual and physical. He will attempt very difficult, even impossible, tasks, and feel that he accomplishes them. And he similarly overestimates the productions of others.

Although a stimulant action seems, at first view, so apparent that it has long been held as one of the axioms of therapeutics, and is even now held as true by some eminent pharmacologists, the impartial apparatus of experimental science may be said to have proved the contrary. The evidences of a depressing action of even very small doses of alcohol are almost without number, whilst such phenomena as may be interpreted as true stimulation are due, not to a direct action of alcohol, but to environment, to reflexes, or to depression of inhibitory centers.

If the phenomena be somewhat more closely inquired into, this will become apparent at once. Of the physical phenomena, the **flushing of the cutaneous vessels**—to which the sensation of warmth must be attributed—occurs as the result of a vasomotor paralysis, restricted, it is true, to this area. The **quickened pulse** results partly from reflexes caused by swallowing and by irritation of the mucous membranes, partly from the increased excitement and motion; not at all from a direct action on the cardiac nervous or muscular mechanism—for it is entirely absent in animals, and very brief in man if the factor of excitement be eliminated. The same is true of the **quickening of respiration.**

Binz and his school lay great stress upon an increase of respiration, both in number and depth, especially prominent in fatigue. This occurs even during sleep, so that it is not the result of increased motion. But it may be fairly considered a reflex,—mustard oil produces a similar result,—and besides, it seems to have a more intimate connection with the volatile substances constituting the "bouquet"—the flavor of wines and liquors—than with the alcohol itself.

The **psychic phenomena** find their explanation in a dulling of certain mental faculties whilst others are still practically unaffected—in a disturbance of what has been called the "normal balance of the brain." The first functions to be lost are the finer grades of judgment, reflection, observation, and attention—the faculties which have largely been acquired through education, and which constitute the elements of the restraint and prudence which man usually imposes on his actions.

Thus, to quote a well-known example: The orator no longer considers that he may be called to account for his utterances; he allows himself to be carried by the impulse of the moment, without reflecting on ultimate consequences, and, as his expressions become freer, they acquire an appearance of warmth, of feeling, of inspiration. And not a little of this inspiration is contributed by the audience, who are usually in a similar condition of increased appreciation.

The view that alcohol increases the intellectual and physical powers of the individual is shown by actual experiment to be erroneous, and based almost entirely upon the subjective conditions of the individual, his weakened faculty of judgment.

Ergographic experiments show that moderate doses (10 Gm.) at first increase the power of voluntary muscular work (to 9%), but in one-half hour diminish it to 6% below normal. The increase is only seen when the muscle is not too much exhausted; the alcohol appears to be itself incapable of furnishing the requisite energy. This effect is entirely central. The muscle itself, and the endings, are more readily exhausted from the start. Similar observations have been made on the frog, where the "tonic" influence appears to be confined to the nerve endings.

Kraepelin, who has probably done the most extensive accurate work on the psychic effects of alcohol, states it as his opinion that the association of words and ideas is favored by it, but that the rapid association of disconnected syllables, as in psychologic experiments, is diminished.

Experience soon teaches this lesson: that alcohol does not really stimulate. Persons who have to undergo severe exertion, either physical or intellectual, very rarely take alcohol before or during their labor, but only when this is finished. And then not for any stimulating, but really for its depressing, effect; for the feeling of comfort and general relaxation which it induces. The continued use of large doses of alcohol will, of course, diminish the activity of the individual.

Another very characteristic feature, evidently resulting from this paralysis of the higher functions, is the *loss of the power to control words*. There may be causeless merriment or sadness, friendliness or the opposite. It is interesting to note how often alcohol brings out the true character of an individual by this abolition of restraint: "There is truth in wine." On the other hand, the habits of self-control, where they have been cultivated, persist to some extent even in intoxication.

These facts being established, it may be asked: *Why do we continue to speak of alcohol as a stimulant?* How may the undoubted benefits in general debility, in shock, in high fever, etc., be reconciled with the view that alcohol does not stimulate the central nervous system? The answer must be that the explanation is not the same in all cases, but that it is in no case necessary to assume any *direct* stimulant action. This will be discussed in the therapeutic part (p. 427).

II. PARALYTIC STAGES.

The symptoms of the first stage being so largely paralytic, it is plain that no sharp line can be drawn between it and the second stage; and, similarly, there is a very gradual transition between the second and third; all the stages, in fact, being but periods in the same progressive paralytic process.

The **narcotic stage** may be said to exist when the symptoms of lessened psychic activity assume prominence. *Sensation* and *motion* become lessened. *Speech* is thick and muttering, the *gait* uncertain, the *special senses* are blunted. There is tendency to *sleep.*

Consciousness and sensation are gradually completely abolished, and this constitutes the third or **anesthetic stage.**

In the **paralytic stage** proper, the *symptoms* are those *of beginning medullary paralysis:* The *respiration* is slow and stertorous, the pulse scarcely discernible. *Skin* cold and cyanotic. *Pupils* generally dilated. *Reflexes* abolished. If very large doses have been taken on an empty stomach, these paralytic symptoms come on at once. **Fatal cases** from acute poisoning are very rare: in these the coma grows deeper, and death finally results, usually from edema of the lungs or stoppage of respiration. In **subacute cases** it may occur suddenly during convalescence as a result of the gastric irritation, or from the debilitation. The fatal dose is stated as 60 to 180 Gm.

Ordinarily, however, the course is very slow, and almost always ends in **recovery.** The coma—if the intoxication has progressed so far—passes into natural sleep, and on awakening there follows a series of symptoms pointing mainly to *acute gastric catarrh*, and grouped by the Germans under the name of "Katzenjammer": headache, coated tongue, loss of appetite, irritable stomach, muscular pains, etc. These show curious peculiarities for the various alcoholic liquids.

Directing more particular attention to the **effects upon the medullary centers,** a primary direct paralysis may be made out, although, as has been said, this may be preceded by reflex stimulation. Normally and when no excitement is present, the *respiration* is slowed. As to the **circulation,** the *heart* is unaltered in rate, or later slowed and lessened in efficiency, due to a direct muscular effect. The *vasomotor system* is not affected by moderate doses, except that the cutaneous vessels show quite a marked dilatation, which is of considerable therapeutic import. Its mechanism is not known. A dilatation of the vessels of the stomach is due to a local irritant action. The area involved in the vasodilatation is not sufficiently extensive to effect any fall in *blood pressure*, which remains unchanged. In the fourth stage there is a paralysis of the vasomotor, as of all other medullary centers; and consequently a fall of blood pressure.

These remarks upon the action of alcohol on the circulation apply only to the normal individual. With *debilitated individuals* it may markedly raise the rate and efficiency of the heart, and consequently the blood pressure, probably mainly by acting as a food.

As a consequence of the cutaneous vasodilatation, there is a *fall in the temperature* of the body, especially when the external temperature is low. At the same time there is a sensation of warmth, and an actual rise of the temperature of the skin, through this increased cutaneous circulation.

III. EFFECTS OF ADMIXTURE OF OTHER SUBSTANCES (ETHERS, ETC.).

Before leaving the actions of alcohol on the central nervous system, some peculiarity of action possessed by the different forms of spirits may be discussed. These divergences from the typical effects are due mainly to substances other than alcohol, but for the most part not known.

Beer owes its marked *hypnotic qualities* to the lupulin of the hops as well as to the alcohol. Some wines are also hypnotic, whilst others—the majority—are exalting.

The *diuretic action of* **gin** is largely due to the essential oils contained in it. Partially fermented wines produce particularly often a disturbance of the equilibrium, sometimes seen with other forms of spirit—the individual becomes "knee drunk," *i. e.*, incapable of maintaining the upright position, before the paralysis of the mental functions has progressed to a great extent. **Absinthe** produces hallucinations and finally epilepsy.

The **stronger spirits** contain, besides alcohol, substances which may pharmacologically be divided into two groups: those that give the bouquet (flavor) and have no other marked action; and those that have a deleterious effect. The latter—which are commonly called impurities—are largely destroyed by age. The most common is amyl alcohol (fusel oil).

The action of these, as far as studied, is, upon the whole, similar to that of alcohol itself, but more toxic. The *higher ethers* are said to be more stimulant to respiration. The *aldehyds* have a strongly irritant action on mucous membrane—as shown by formaldehyd or acrolein (allyl-aldehyde—the vapors of overheated fatty oil). The relative toxicity of the higher alcohols has already been given (p. 414). The most important is *amyl alcohol*, the so-called *fusel oil*. It has a more violent acute action and more pronounced after-effect than the ethyl alcohol. But its admixture up to 1 % produces very little difference in acute intoxication. *Furfurol*, which was formerly believed to modify the nature of the intoxication, does not appear to do so. But it must be said that this whole subject is much in need of thorough investigation.

Natural strong spirits contain the following amounts of these ethers, etc.:

	ALCOHOL.	FORMIC ACID.	ACETIC ACID.	BUTYRIC ACID.	CAPRIC ACID.	ETHYL FORMATE.	ETHYL ACETATE.	ETHYL BUTYRATE.	ETHYL CAPRATE.
French Brandy . . .	49.75	0	0.032	0.001	0.004	0	0.094	0.001	0.010
California Brandy . .	45.83	0	0.031	0.002	0.003	0	0.043	0.004	0.008
Jamaica Rum	67.08	0.010	0.103	0.005	0.012	0.022	0.695	0.009	0.031
Batavia Arac	50.83	0.014	0.157	0.007	0.009	0.011	0.245	0.009	0.012

Artificial liquors are made by the admixture of ethers and essential oils to alcohol. Their action is not uniform, but it is generally more irritating locally, and more injurious to the brain.

IV. THEORIES OF THE ACTION OF ALCOHOL.

Alcohol and the members of this group are amongst the very few drugs with which it has been attempted to reach the real explanation of the phenomena, and to go behind the bare statement that they act stimulatingly or depressingly on such and such structures. A number of hypotheses have been advanced, but the question cannot be considered as conclusively answered.

In the first place, it was suggested that these narcotics *rendered the blood incapable of nourishing the brain*, in some mysterious manner. But since chloroform acts upon a frog whose brain has previously been deprived of all nourishment by replacing its blood with normal salt solution, this theory cannot stand. The same objection holds against the theory that the narcosis is produced by insufficient nourishment of the brain through *disturbances in its circulation*. Nor are all observers agreed on just what these changes are; they must be looked upon as incidental rather than causative. They are due probably to the effects of alcohol on the circulation elsewhere—the dilatation of the splanchnic and cutaneous vessels, etc. It must be considered as proved that these narcotics act directly upon the nerve-cells. In regard to this, there are three main theories, two based upon chemic, the other upon histologic, evidence.

Binz believed that there is an actual *coagulation of the protoplasm of the cell*. This view seems unsupported by any evidence, and it is very doubtful whether protoplasm, once it is coagulated, could ever again become functionally active. The second theory, that of Meyer and Baum, seems, upon the whole, the most acceptable. According to this, the narcotics act by virtue of their *affinity for fats*. It is well known that they are much more soluble in fat than in water; and these authors assume that they enter into solution in the fat of the cell, displacing its water. In support of this view they point out that the strength of the narcotic action is proportional to the solubility in fat. A cell in which the water is replaced largely by this foreign substance cannot likely functionate in a normal manner, whilst it may be easily understood how they may return to normal once the foreign substance is again excreted. According to this theory, any substance soluble in fat would act as a narcotic, and this is indeed the case. Since nervous tissue is especially rich in fat, it is also easily understood why, on this theory, there should be a selective action for this tissue.

The laking of red corpuscles which they produce seems to depend upon a solution of the stroma, brought about in a similar manner.

A last theory is based upon changes in the *histologic* appearances (Nissl method) of the nerve-cells in acute and chronic alcohol-poisoning (fusion and diminution of the granules, Fig. 69). The dendrites of many pyramidal cells show moniliform enlargements. These changes have completely disappeared in forty-eight hours, even when caused by chloroform anesthesia lasting nine hours. These phenomena do not conflict with Meyer's view, that the changes are caused by the displacement of water by the narcotic. The hypothesis which had been advanced, that the narcosis depends upon a retraction of the dendritic processes, appears to be based at present purely on speculation.

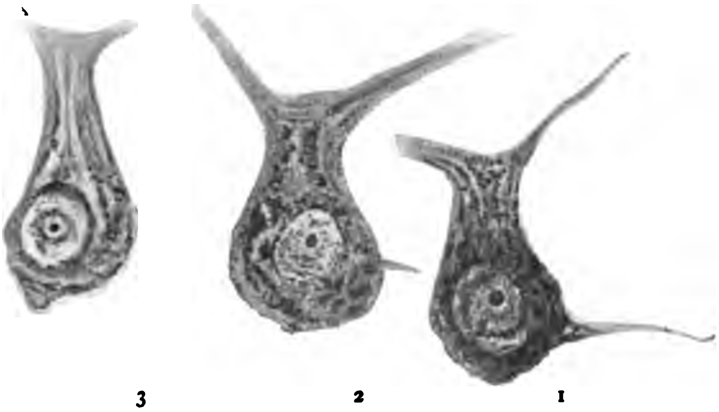

Fig. 69.—Alcohol on Purkinje cells, cat—Nissl stain (after C. C. Stewart): 1, Normal; 2, alcohol for fifty minutes; 3, for fifty-four hours.

V. ACTION UPON PARTICULAR FUNCTIONS.

On account of the great importance attaching to the use and action of alcohol in ordinary doses, it will be useful to summarize again what is known concerning its influence upon particular functions.

1. Influence of Alcohol upon Digestion. — Alcohol could be conceived as influencing the process of digestion by acting on the ferments, on secretion, on the movements of the alimentary canal, or on absorption. And, in fact, it acts in all of these ways. (All the different alcohols agree qualitatively in their action on these functions.)

(**a**) **Action on Ferments.**—Since alcohol is very readily absorbed, and no great amount of it reaches the intestine, it can only influence the ferments of the stomach, and its action on pepsin is alone of practical interest. It is found that *in vitro*—and there is no reason to suppose that it acts any differently *intra vitam*—

1% to 2% of alcohol increases the rapidity of peptic digestion.
Up to 15%, it causes no perceptible retardation.
15% to 18%: the digestion is reduced by one-fourth to one-third.
20%: the digestion is strongly inhibited.

Beers and wines have a slightly more unfavorable effect on account of the extractive matter contained in them.

(**b**) **Effect upon Secretion of Digestive Juices.**—Here also saliva and gastric juice need alone concern us.

Saliva: The presence of alcohol, strong or dilute, in the mouth increases the amount and the solids of the saliva, just as do many other substances (acetic acid, ether, etc.). This increased secretion does not take place if the alcohol is introduced directly into the stomach through a fistula.

Gastric Juice: The amount, the acidity, and the solids are very markedly increased, even when the alcohol does not come into direct contact with the gastric mucous membrane, but is introduced directly into the intestine. This juice is strongly proteolytic.

(**c**) **Movements of Alimentary Canal.**—These show a quickening.

(**d**) **Effect upon Absorption.**—The alcohol itself is very rapidly absorbed: 50 c.c. of a 20% alcohol disappear from the stomach of a dog in less than half an hour; and with the duodenum ligated, 200 c.c. of a 37% alcohol are completely absorbed from the stomach in three to three and a half hours. The absorption of other substances is also favored by it.

The effects upon the digestive organs are all merely expressions of its *local irritant action:* This produces, in mild stages, increased vascularity; and, partly as a result of this, partly through a direct action upon the cells, an increase of secretion, of movement, and of absorption.

In **severer grades**—such as are produced by the stronger spirits—it causes vomiting and diarrhea, and if used continuously, chronic gastric catarrh.

To sum up, then, the experimental data bearing upon the effects of moderate doses:

The action of alcohol on digestion is a purely local one. Only gastric digestion need be considered, since the alcohol does not reach the intestine.

Moderate amounts tend to favor the process of digestion through an increased secretion of proteolytic juice, through increased gastric movement and increased absorption. With a percentage of alcohol above 15, these are counteracted by the lessened ferment action.

The actual result will depend upon which of these two—the beneficial irritant or the deleterious anti-ferment action—predominates. Actual experiments on *intra vitam* digestion are not yet sufficiently numerous. But as far as they go, they show that in the dog the time required for the digestion of meat is about the same with and without alcohol; and metabolism experiments in man also prove that it does not diminish the utilization of food.

Small amounts of weak alcohol taken at meals cannot, therefore, have a bad effect upon digestion, and may even act favorably. The alcohol should not be taken in strength greater than perhaps 20%: even this would be too strong did it remain for any length of time; but it is absorbed so rapidly that this strength would very soon reach the favorable limit.

Large quantities of alcohol, however,—and especially when in concentrated form,—produce an irritation which surpasses the physiologic limit and interferes with the functions; and this is seen most markedly in chronic cases.

2. **Fate of Alcohol after Absorption.**—A question which attaches itself closely to the effect of alcohol upon digestion is that of its fate after absorption; or, as the question is usually put: *Is it a food* or a poison? Is it used up in the economy, or does it act as a foreign body?

The answer must be: both.

All the effects so far studied go to show that it always acts as a poison or as a foreign body. The extent to which it acts as a food depends upon complicated conditions:

Only a small part (less than 10%) of the alcohol is ordinarily **excreted** unchanged. The exact amount varies with the quantity taken.

With medicinal doses, the amount excreted through:

Lungs = 0.5% to 6%;
Kidneys = at most 1% to 2½%;
Skin and Intestines = none.

To this may be added a very small amount (to 0.3%) in the milk, if the quantity taken is very large; none, if moderate. Alcohol may be demonstrated in the blood for twenty-four hours after intervenous injection of large doses.

The unexcreted alcohol must be oxidized, with the ultimate production of CO_2 and H_2O, and the *liberation of energy*. It has been contended by some that the energy so liberated is not utilized in the body: that it is used up in the production of heat, and is lost. But it has been definitely shown that it does not lead to an increase of O consumption or CO_2 production. It must, therefore, take the place to a certain extent of the ordinary sources of energy—carbohydrates and fats. To this may be added a further saving of energy from lessened movement when the alcohol has a quieting effect. But alcohol is not a perfect substitute for carbohydrates and fats; for the latter may to some extent replace the nitrogen of the diet, whilst alcohol does not appear to possess this property: If alcohol is substituted for carbohydrates or fats, it leads to a loss of nitrogen, and it effects no saving if added to the ordinary diet. The other hydrocarbon narcotics act similarly.[1]

It has, indeed, been claimed that if alcohol saves fat and fat saves proteid, then alcohol must save proteid. The fallacy of this reasoning lies in supposing that the nitrogen is consumed as a source of energy: this is only incidental, the main consumption being in what might be called "wear and tear of machinery." Now, of two samples of coal, furnishing an equal amount of energy, one may be much more wearing to the engine. And, similarly, although fat and alcohol both furnish energy, the former, at the same time, saves the nitrogenous molecule, whereas the latter wastes it.

Briefly, then, alcohol can to a certain extent take the place of carbohydrates and fats in food; or where the diet is insufficient, it will save these constituents of the body. In this case—*where the diet is insufficient*, whether this be from insufficient supply, from faulty digestion, or from extraordinary consumption—the food value of alcohol is considerable.

When, on the other hand, *the food-supply is ample*, this combustion of alcohol is harmful. For it then prevents the complete combustion of the ordinary foods; and the incompletely oxidized waste products are then excreted, and are in this way lost to the organism; or they are retained, and then favor the development of fatty degeneration of various organs.

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[1] Other observers claim that alcohol saves nitrogen, when the body has grown accustomed to it. The bulk of the evidence seems to be in favor of the view given in the text.

The **actual observations** on the effect of alcohol in moderate doses on nutrition have led to the following conclusions:

1. With a diet on which the individual gains in weight, the addition of alcohol lowers the rate of increase.
2. When added to a diet on which the weight remained constant, it tends to cause a loss of weight.
3. With insufficient diet, it lessens the loss of weight, or may even cause a gain.

VI. THERAPEUTICS OF ALCOHOL.

The most frequent internal use of alcohol is that of a "stimulant," using the term in its practical meaning. That the nature of this stimulation is not the same in all cases is sufficiently indicated by the fact that it is used in three very different conditions: in shock, in fever, and in debility. The manner in which the stimulation is brought about in these cases requires some further elucidation in order that the drug may be rationally employed.

1. In Shock, *especially traumatic; Hemorrhage; Sudden Weakening of the Heart; Snake-bite, etc.*—The value of alcohol in these conditions can scarcely be doubted. Its explanation is quite complex, since it acts in a number of ways:

(*a*) By producing an analgesia, at least partial; and, at the same time, its psychic effect—the more cheerful and courageous condition of mind which it induces—is of value.

(*b*) By the depression of the central nervous system which it produces in larger doses. Depressed centers are not so subject to shock, as is shown by the fact that extensive operations are much less apt to produce this condition under anesthesia.

(*c*) By a genuine reflex stimulation: With the usual way of taking the spirit, this occurs from the mucous membrane of the mouth and stomach. The same reflex stimulation may be obtained through the nose; spirit of ether is especially useful in this connection; and the smelling-salts also owe their action in part to alcohol. A more powerful reflex stimulation may be obtained by the hypodermic injection of alcohol or of ether, or of spirits of camphor (one or two syringes).

The stronger preparations of alcohol are the best for this purpose.

2. **Use in Fever,** *Chills, Inflammatory Conditions, etc.*—Alcohol acts here in the following manner:

(*a*) Through dilatation of the cutaneous vessels (see p. 303 and Chap. XXI, C). This increases the loss of heat, removes blood from congested internal organs, and lessens the resistance to the work of the heart. This temporary relief of the heart is often all that is required to restore its powers, and the pulse will become more regular and stronger. The antipyretic action is not very lasting.

This action on the cutaneous vessels is possessed in still greater degree by Sp. Æther. Nitr., which in so far may take its place.

(*b*) Through its narcotic action, counteracting the nervous phenomena of fever and inducing quiet and rest. This in turn diminishes the demands made upon the strength of the patient.

(*c*) Its action as a food: The metabolism in fever is very greatly increased, and the assimilative powers at the same time diminished. Whilst this increased tax falls very largely upon the nitrogenous part of the body, the drain upon the carbohydrates and fats is also very serious. And these last can be met very largely by alcohol, which possesses the advantage over ordinary foods of very ready absorption.

(*d*) The diuresis may be useful in removing toxins, etc.

The employment of alcohol in fever must still be looked upon as largely empirical; for it is impossible to tell *a priori* to what point its depressing action on the central nervous system will be useful and where it will begin to be detrimental. The individual observations in each case can alone guide its employment: As long as it improves the prominent symptoms, the dose may be increased. As soon as it ceases to do so, it should be diminished or stopped. It is frequently astonishing to see the quantity which is borne without harm in fever and without producing "intoxication." This must be attributed largely to its more rapid oxidation. The amount given must, of course, also be governed by the previous habits of the patient.

With regard to the use of alcohol against chills and exposure, it must be reiterated that the time for taking it is after, not during, the exposure. If the latter is done, whilst it causes a temporary relief and feeling of warmth, this is obtained at the expense of an increased loss of heat, and consequently diminished power of resistance. But if taken after the exposure, the dilatation of the cutaneous vessels favors the absorption of external heat, and also prevents the tendency to congestion of internal organs.

In all these conditions the alcohol is taken as concentrated spirits, diluted with at least equal amounts of water.

Alcohol should not be used in nephritis.

3. **In Convalescence and General Debility.** — The underlying conditions are here so obscure that no etiologic treatment can be employed. There is, in fact, no organic lesion, and in all such cases a great deal may be expected from improving the symptoms. This, like nursing and hygiene, increases the comfort and well-being of the patient, and starts him on the way to improvement. Alcohol meets these indications in an excellent manner: The feeling of well-being caused by it, the enjoyment in the act of taking it, the rest and sleep induced by its narcotic action, its food-value and its beneficial effects upon digestion, all concur in its action. To this may be added its slight but certain effects upon the vascular system,—the altered distribution of blood, the diminished resistance to the heart,—which may be of benefit in some cases.

For these purposes, alcohol is usually taken in the form of light wines.

4. **The narcotic and hypnotic effects** of alcohol are also utilized, the former in melancholia, neuralgia, and some other obscure nervous diseases; the latter in insomnia. Whilst the effects are undoubtedly beneficial, there exists a very great danger of inducing chronic alcoholism, especially in the first class of cases. It must certainly be used with very great caution. The stronger spirits are best adapted for obtaining the narcotic effect; beer, for the hypnotic.

5. **Indigestion.**—From what was said on page 425 it will be easily understood that it does not act equally well in all cases. Whilst the clinical interpretation of the various forms of indigestion is not as yet so perfect as to enable us to tell the pathology of those cases in which alcohol is useful or not, it might be expected to be of benefit where there

is a faulty circulation, whilst it would be harmful where the amount of ferment secreted is small and not capable of increase. Certain wines become injurious on account of their acidity. Those wines containing tannin—and this includes especially the red wines—are detrimental to digestion in virtue of this. They are sometimes used against diarrhea on account of their astringent properties. Brandy is also used against diarrhea. This probably rests upon the beneficial effects of an increased circulation.

Champagne is also used as an antemetic. Its action in this case depends upon the CO_2 rather than on the alcohol.

As **contraindications** to the internal use of alcohol may be mentioned:

The danger of forming a habit.
Gastric irritation.
Urethral disease or nephritis.

6. The *local actions* of alcohol are also frequently used. The cooling produced by its evaporation is very grateful in *fever*, and it is frequently used for sponging the skin. The local use of alcohol is of further benefit in this condition by preventing the development of bedsores through its mild irritant action. The same property determines its use on ulcers. Used in a more concentrated form and kept from evaporating, it acts as an excellent rubefacient, and, in the form of tinctures, it forms an important ingredient of most liniments.

It is scarcely necessary to refer to the great pharmaceutic importance of alcohol, depending upon its solvent powers. It must be remembered that it forms an ingredient of very many pharmaceutic products—tinctures, fluid extracts, and spirits.

VII. HABITUAL USE OF ALCOHOL.

It may be considered as proved—some authorities to the contrary notwithstanding—that a certain amount of alcohol (variable in individual cases) may be taken daily without any demonstrable permanently injurious effect. But it stands equally certain that it is as dispensable to the organism as nicotin or caffein, and that it must be looked upon purely as a luxury. The injury done by such use of alcohol lies alone in the fact that it is so apt to lead to the use of immoderate amounts.

With such excessive use a train of phenomena results, which may be grouped together under the name of chronic alcoholism, and which depend in part upon the irritant action of the alcohol, in part upon specific injury to the neurons.

The first effects are *local*, and depend largely upon the concentration of the spirits. They consist of a *catarrh of the whole alimentary canal*, progressing from the pharynx downward. They are characterized by the usual symptoms of catarrhal gastro-enteritis: loss of appetite, gastric distress, irregularity of stools, longing for spices, etc. The chronic catarrh leads to malnutrition and emaciation when strong spirits are used. It also appears to constitute a predisposing factor to carcinoma of these organs. In the case of excessive beer-drinking the habitual overdistention of the stomach leads to chronic dilatation.

The continued presence of alcohol in the body sets up a series of *irritant and degenerative phenomena in various other organs* with which it comes in contact. These changes consist in fatty infiltrations, cellular degenerations, and hypertrophy of connective tissue. The necrotic changes in the tissue cells must be attributed to the continued irritation from the constant presence of the alcohol; and to this must be added the interference with circulation due to the changes which alcohol causes in the blood-vessels. These two—the direct irritant action of alcohol on the cells, and the impaired circulation—are inseparably connected in the production of the degenerations. Of these, the fatty are the most common, since alcohol, by its combustion, prevents the normal consumption of fat. Connective-tissue formation results as the ordinary consequence of necrosis of the parenchyma.

These changes are proportional to the *concentration* of the alcohol. And since this is naturally greatest in the liver, kidneys, and blood-vessels, these organs show the action first and most prominently. And in the liver, again, the *periphery of the lobules* is mainly affected, on account of the anatomic relation to the portal vein.[1]

Next in point of time comes the action on the *blood-vessels*. This is of especial import, since it contributes materially to the degenerations in other organs. The principal changes are in the intima: there are fatty degenerations, loss of elasticity, and atheroma. These may lead to ruptures (apoplexy, etc.).

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[1] It is claimed that the degeneration of the liver can be avoided in animals by the administration of cane-sugar.

The degenerative changes in the *kidneys* lead to nephritis, with cirrhosis, albuminuria, diminished secretion of urine, secondary weakening of the heart, etc. The *heart* itself, however, in common with skeletal muscle, shows primary fatty degeneration. This, together with the atheroma, etc., leads to hypertrophy and dilatation of the viscus, and later to dropsies, etc. The fatty changes in *voluntary muscle* lead to muscular debility, especially in beer-drinkers, in whom there is more material for fat formation.

The *respiratory organs* show a chronic catarrhal inflammation of the passages, and a disposition to fatal pneumonia. Changes in the skin—vascular ecchymoses, acne rosacea, disposition to furuncles and carbuncles—may be counted amongst the earlier actions.

These various anatomic lesions of important organs result in a pronounced lowering of the "powers of resistance," and a high mortality with infectious diseases, operations, etc. Part of this may be due to a lowered alkalinity of the tissues through the partial oxidation of alcohol into fatty acids.

The effects of chronic alcoholism upon the **central nervous system** differ from the above in that they are partly functional. Too great stress cannot be laid upon the importance of habit and repeated impressions on the psychic activities. The constant repetition of the features of alcoholic excess could not but produce in this manner a permanent moral degeneration. But associated with this functional feature are marked organic changes, due to the same causes as similar changes in other organs; and, lastly, it must be remembered that alcohol has a specific action on the nerve-cells.

Amongst the organic lesions which have been observed are: Chronic meningitis with thickening; serous effusions into ventricles; softening; tendency to hemorrhages and apoplexy. Histologically, shrinkage and alterations in the staining properties of the cells (Fig. 69) and changes in the dendritic processes have been averred.

Clinically, the first effects are shown by a diminished activity of the individual. This occurs even with very moderate doses. Later there is a diminished acumen of the special senses and of the reasoning powers, leading, the former to disturbances of vision, the latter to degeneracy and dementia, often suicidal. It is a noteworthy fact that by far the greater proportion of inmates of insane asylums and prisons were addicted to the excessive use of alcohol. In how far alcohol is responsible for the population of these institutions —whether the abuse of alcohol is really the cause of these conditions or only another effect of the underlying disease —cannot be decided at present.

On the part of the motor system there are tremors, and later convulsions and paralyses, the latter partly the result of peripheral neurites.

The influence of alcoholism in the parent on the *offspring* is a question not yet definitely answered. It is certain that the nutrition and resisting power of the offspring are greatly impaired by it. The mortality amongst the children of alcoholics is very high. It is also certain that psychic degeneracy—epilepsy, idiocy, predisposition to crime and to the abuse of alcohol—are extremely common in them. But it cannot be decided whether it is the degeneration induced in the parent by alcohol, or the degeneration underlying the abuse of alcohol, that is inherited. The latter is the more likely.

When alcohol is taken by the mother, it passes across the placenta in such amount as to exist in the same concentration in the blood of the fetus as in that of the mother.

Alcohol is not the only member of the hydrocarbon series which has been abused as an intoxicant. Ether, chloroform, chloral, and even turpentine and gasoline have their devotees. Their effects, in so far as they have been studied, correspond closely to those of alcohol.

VIII. TREATMENT.

The *treatment of acute alcoholism* consists in evacuation of the stomach and nervous stimulants, caffein or strychnin. The subsequent headache and nervousness are met by bromids.

Chronic alcoholism can only be treated by withdrawal of the drug. Medication is of use only in meeting the symptoms. Irritants—especially capsicum—are useful in replacing the local action of alcohol; the depression should be met by caffein, the insomnia by bromids. Suggestion may be very useful.

IX. DELIRIUM TREMENS.

A peculiar disease, specifically characteristic of chronic alcoholism, remains to be mentioned, namely *delirium tremens*. This occurs in chronic alcoholics whenever their forces are unusually weakened—by an extraordinary excess or by the suppression of their usual allowance of alcohol; by absence of food; by exposure or overexertion; by an operation, etc. The symptoms consist in violent tremor, persistent insomnia, and hallucinations of a terrifying character. It usually runs its course in a few days. The main indications of treatment are to support the strength of the patient and to combat the excitement and insomnia by hypnotics, as bromids, chloral, or opium. It is not deemed advisable to withdraw the alcohol entirely during this condition.

X. MATERIA MEDICA.

Preparation of Alcoholic Liquids.—Alcohol is a product of the alcoholic or vinous fermentation of liquids containing certain sugars (especially dextrose). This fermentation is produced by the growth of the yeast plant—*Torula cerevisia*. This occurs best at temperatures between 15° and 32° C. (60° to 90° F.). Other sugars, dextrin, and starch are not directly fermentable, but are first converted into dextrose:

$$\underset{\text{Starch}}{3C_6H_{10}O_5} + H_2O = \underset{\text{Dextrin}}{2C_6H_{10}O_5} + \underset{\text{Dextrose}}{C_6H_{12}O_6}.$$

$$\underset{\text{Starch}}{3C_6H_{10}O_5} + 2H_2O = \underset{\text{Maltose}}{C_{12}H_{22}O_{11}} + \underset{\text{Dextrose}}{C_6H_{12}O_6}.$$

$$\underset{\text{Dextrin}}{2C_6H_{10}O_5} + 2H_2O = \underset{\text{Dextrose}}{2C_6H_{12}O_6}.$$

$$\underset{\text{Maltose}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{Dextrose}}{2C_6H_{12}O_6}.$$

In this fermentation the greater part of the Dextrose is changed into alcohol and CO_2:

$$C_6H_{12}O_6 = 2CO_2 + 2C_2H_6O.$$

The reaction is not as simple as this equation would indicate: besides CO_2 and C_2H_6O, various other products are formed,—glycerin, succinic acid, and others as yet unisolated,—which aid in giving the flavor to the resulting liquids. This is in part due, however, to substances other than sugar, present in the original liquids.

It was formerly supposed that the bouquet of the different sorts of wines, etc., depended upon differences in the constituents of the grape-juice; but it is now known that they are caused rather by differences in the yeasts infesting these grapes. The inoculation of a barley infusion with a wine yeast gives to the fermented liquid the peculiar flavor of that particular wine (the so-called "Malton Wines").

As ordinarily prepared, however, the character of the fermented liquids depends upon their origin. When made from barley, they are beer, etc.; from apples, cider; from grapes, wine; from milk, kumiss, etc.

Most of these, as well as the distilled spirits, undergo further chemic changes on keeping, resulting in the destruction of undesirable constituents ("impurities"—fusel oil, etc.) and in the development of ethers, etc., imparting a finer flavor to the liquid.

The alcoholic fermentation only progresses to a certain point; beyond this, it is either arrested entirely, as soon as the proportion of alcohol exceeds a certain amount; or it passes into acetic fermentation, with the conversion of the alcohol into acetic acid.

When these weak liquids are subjected to distillation ("rectification"), the stronger "alcoholic liquors" result. These receive different names according to their origin:

Whisky, when distilled from fermented grain (this rectified over juniper berries is *Holland Gin;* over turpentine, *Common Gin*); from wine, *Brandy* (*Cognac*); from molasses, *Rum;* from rice, *Arrack*, etc.

Their alcoholic strength is about as follows:

	Percentage by Volume.	Weight.
Whisky	50 to 60	42 to 52
Brandy	55	47
Rum	50	42
Gin	48	40
German "Schnapps"	45	38
Russian "Dobry Wutky"	62	54

Further redistillations result in the official alcohol; and by redistilling from some hygroscopic substance, usually quick-lime or calcium chlorid, the so-called "Absolute Alcohol" is obtained.

The strength of alcoholic liquids is deduced from the specific gravity after distillation.

	Specific Gravity. (15.6° C.) (60° F.)	Per Cent. Weight.	Per Cent. Volume.
(A) Pure Alcohols:			
⁂ **Alcohol** (U.S.P.) [Spiritus Rectificatus, B.P.]	0.820 (U.S.P.) 0.834 (B.P.)	91.0	94.0
Alcohol Absolutum (U S.P., B.P.). Not more than 1% by weight of water. Boiling-point, 78.4	0.797	99.0+	
Alcohol Deodoratum (U.S.P.). Alcohol in which the fusel oil, etc., has been destroyed (as by permanganate). Same properties as alcohol		92.5	95.1
⁂ **Alcohol Dilutum** (U.S.P.). Made by mixing equal measures of alcohol and water	0.938	41.0	48.6
Alcohol (70%) (B.P.). Made by mixing 100 vol. of alcohol (90%) with 31 vol. of water	0.8900		70.0
Alcohol (60%) (B.P.). Made by mixing 100 vol. of alcohol (90%) with 53.65 vol. of water	0.9135		60.0
Alcohol (45%) (B.P.). Made by mixing 100 vol. of alcohol (90%) with 105.34 vol. of water	0.9436		45.0
Alcohol (20%) (B.P.). Made by mixing 100 vol. of alcohol (90%) with 355 8 vol. of water	0.9760		20.0

Since a condensation occurs on mixing alcohol and water, the percentage of the resulting product cannot be deduced by the formula $\frac{\%}{V + V}$.

The most important preparations are marked ⁂.

The quantities needed to make the most common dilutions are the following:

TO MAKE 100 C.C. OF:	USE *Official* (U.S.P.) ALCOHOL:	WATER:	SPECIFIC GRAVITY. (15.6° C.) (60° F.)
80% (volume)	85.5 c.c.	16.0 c.c.	0.8642
70%	73.5 c.c.	29.0 c.c.	0.8903
60%	63.5 c.c.	39.0 c.c.	0.9135
50%	53.5 c.c.	49.5 c.c.	0.9344
40%	43.0 c.c.	60.0 c.c.	0.9520
20%	21.3 c.c.	73.5 c.c.	0.9759

(B) Stronger Spirits:

The strength of the more important has been indicated on page 435. The following are official:

*** *Spiritus Frumenti* (U.S.P.).—*Whisky.*—At least two years old; 44% to 50% by weight of alcohol (50% to 58% vol.). Sp. gr., 0.917 to 0.930.

*** *Spiritus Vini Gallici* (U.S.P., B.P.).—*Brandy.*—At least four years old; 39% to 47% by weight of alcohol (46% to 55% vol.). Sp. gr., 0.925 to 0.941.

Mistura Spiritus Vini Gallici (B.P.).—Four ounces each of brandy and cinnamon water, two yolks of eggs, and ½ ounce of sugar.

(C) Weaker Alcoholic Liquids:

The only ones official are:

Vinum Album (U.S.P.).—*White Wine.*—A dry white wine, such as Catawba. 10% to 14% by weight of alcohol.

Vinum Rubrum (U.S P.) —*Red Wine.*—Dry red wine such as native Claret or Burgundy. 10% to 14% by weight of alcohol.

Vinum Xericum (B.P.).—Sherry.—A pale wine containing not less than 16% by volume of alcohol.

Wines are made by fermenting the expressed juice (must) of the grape. If this contains the skins of dark grapes, the wine will be red; if made from light grapes, or from the juice of dark grapes without skins, it is "white"; *i. e.*, an amber color.

A wine which contains much alcohol (15% to 20%) is "generous"; one poor in alcohol, "light"; one containing much sugar, "sweet"; poor in sugar, "dry." If it contains CO_2, it is "sparkling"; if tannin, "rough" or "astringent"; if acid tartrates, "acidulous." The last two ingredients will interfere with digestion if the wine is habitually used.

The most important wines are:	ALCOHOL. Per Cent. Weight.	ALCOHOL. Per Cent. Volume.
Sherry (Vinum Xericum): Dark amber, dry, little acidity (*Madeira*, Marsala, Tokay, Malaga, are similar, but more sweet) . . . . *Port* (Vinum Portense): Deep purple, rather sweet and rough	15 to 19	18 to 23
Claret (Bordeaux): Red, dry, with some degree of acidity and astringency	8 to 14	10 to 17
Champagne: Pale amber, sweet, sparkling . . .	8 to 10	10 to 13
Hock and Moselle: Pale amber, dry, slightly acid	12	15
Catawba: Amber, dry, rather acid (or sweet) .	10 to 12	13 to 15

Unfermented Grape Juice (*i. e.*, must, preserved by heating or an antiseptic) can scarcely be considered a medicinal agent.

The most important preparations are marked ***.

Other Fermented Liquors:

From Apple: *Cider* . .	5 to 10% (by weight).
From Pear: *Perry* . .	
From other fruits	

Malt Liquors.—These contain alcohol, CO_2, sugar, and usually hops. The color varies from pale amber to dark brown, the difference being due mainly to charring of the malt. Lager beer is made by slow fermentation at a low temperature; porter, ale, and stout by rapid fermentation at a higher heat.

Their alcoholic strength is as follows:

Ale, Porter, Stout, and Export Beer	3 to 6%	by weight.
Lager Beer	2 to 3%	

By fermenting milk, a pleasant alcoholic liquid, "*Kumiss,*" can be obtained, which contains to 3% of alcohol.

Mixed Spirits.

It must be remembered that all the alcoholic preparations—Fluid Extracts, Tinctures, Spirits, and Elixirs—whose dose contains more than about 5 c.c. of absolute alcohol show the action of the latter.

Some of the pharmaceutic preparations which are employed largely on account of their content of alcohol are the following:

	Approximate Alcohol Content.
Elixir Aromaticum	25%
Spiritus Juniperi Compositus (a substitute for Holland Gin)	65%
Vinum Ferri Amarum	15%
* *Cordiale Rubi Fructus* (*Blackberry Cordial*), N.F. . .	33%
* *Elixir Adjuvans*, N.F., **Elixir Anisi, and other Elixirs*, N.F.	25%
* *Vinum Aurantii; V. Carnis, etc.; V. Erythroxyli*, etc.	16%

(C) THE CHLOROFORM AND ETHER GROUP.

I. HISTORY.

Attempts to induce anesthesia during operations date back to very ancient times. The Egyptians gave narcotic potions for the purpose. The Assyrians are said to have half strangled the children before circumcision, producing anesthesia by the aid of the CO_2. The Chinese used hashish. All kinds of narcotics were given during the middle ages. But modern anesthesia dates from the middle of the nineteenth century. Its discovery is claimed by quite a number, but the real credit of introducing anesthetics into practice belongs, for ether, to Jackson and Morton, 1846; and for chloroform, to Simpson, in 1847. Soon afterward laughing gas was introduced, although this had been suggested by Davy fifty years before.

II. DETAILS OF ACTION.

The *action* of this subgroup corresponds very closely to the general action which has been discussed on pages 415 to 417.

The *difference from alcohol* consists in the greater rapidity with which the successive stages may be induced. Of the different members of the series which might be used for the production of anesthesia, chloroform and ether alone are important, and the following description applies particularly to them.

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* Not official.

The action of the anesthetics has been divided into *different stages*. Since these are but degrees of the same action, it is quite optional where the line is drawn, and the same stages will be retained here that were given in the discussion of the general action: viz., Stimulant, Narcotic, Anesthetic, and Paralytic.

1. **Stimulant Stage.**—This sets in with a comfortable *feeling of warmth*, spreading over the whole body, soon associated, however, with a *sensation of asphyxia*. The *local effects* make themselves felt by *pricking and smarting of nose, throat, and conjunctiva*. Consequently there is a *hypersecretion of mucus, tears, and saliva*, and *possibly vomiting*; but the latter does not usually occur until much later, when the patient has been some time under deep anesthesia and this is passing off. The *face* at this stage is *flushed*, the *pupils somewhat enlarged*, the *pulse accelerated*, the *respiration somewhat quickened* and irregular—all effects of the excitement.

2. The second or **narcotic stage** is ushered in by formication. The *special senses are disturbed*; there are *hallucinations* (noises, etc.). Sensation of stiffness and want of control in the muscles. The patient loses his *self-control*, and gives way to manifestations which vary with his character—loud talking, laughing, singing, swearing, etc. Then there is *struggling*, and sometimes, especially in hysteric patients, *convulsions*. These motor phenomena are much more violent than in the case of alcohol, probably on account of the greater local irritation and also because of a certain amount of asphyxia. They differ greatly in violence in different individuals. The *skin is moist and warm*, the *face reddened*, the *pupils contracted*, the *apex-beat more pronounced*. The *sensibility to pain* is *blunted*, *but not abolished*.

3. The third or **anesthetic stage**—the stage which it is aimed to produce and maintain—is characterized by complete paralysis of the brain and of the motor reflex centers of the cord, and lowering of the medullary centers. *Consciousness, sensation, and most reflexes* are lost—the *corneal reflex* being among the last. Consequently the muscles are lax. The smooth muscles are not usually affected, but there is sometimes a relaxation of the sphincters. The *pulse is slow, full, and soft*, due to *lowered blood pressure*. The *respiration is slow and shallow*, but *regular*. The *temperature falls* in consequence of the lessened muscular

activity and increased heat loss. The *face* is pale with chloroform, often cyanotic with ether. These symptoms of medullary paralysis do not reach a dangerous degree if the administration is carefully done. But with *prolonged anesthesia* the pulse tends to become progressively weaker, the respiration more shallow, and the temperature lower—it may fall as much as 5° C.

There is some evidence that the sensory cells are paralyzed before the motor, since at certain stages of the action reflex paths which have their sensory and motor cells in different parts of the cord may be excited if the motor, but not the sensory, cells are exposed to the action of the anesthetic. But later the motor cells also lose their irritability. The excitability of the *motor area* of the brain is lowered.

4. The fourth or **paralytic stage** is characterized by progressive paralysis of the medulla. This stage must be carefully guarded against.

The *respiration* becomes irregular, stertorous, labored, and then ceases. The *skin* is cold and pale, and covered with the cold clammy sweat of the "agony." The *pupils* are widely dilated. The *pulse* becomes slow and weak, and ceases normally after the respiration.

5. During the stage of *recovery*, after the anesthetic has been removed, the patient again passes through a stage of excitement, much less violent than in the second stage. Then there is usually a *sleep* lasting for several hours. *Vomiting* is very common during recovery, when the irritation of the alimentary canal is no longer masked by the depression of the centers.

6. Phenomena Indicating Onset of Paralytic Stage.—Since *Accidents in Anesthesia* are generally due to the onset of the paralytic stage,—*i. e.*, to paralysis of the medullary centers,—it is important to study more in detail the symptoms which usher in this condition. It will be profitable to follow these from the beginning of the anesthesia. They refer to the respiration, circulation, and pupil.

Respiration.—This is fairly normal in the *first stage*, except in so far as it is interfered with by the choking produced by the local action. This latter, through stimulation of the trigeminal endings, may also produce a short stoppage, but this is never very long (it does not appear after section of the vagi in animals). During the *second stage* the respiration is affected by the struggling, being alternately stopped and quickened. In the *anesthetic stage* it is very slow, but regular. With the approach of the *fourth stage* it is first quickened as the result of asphyxia. *The danger-sign is the irregularity.* The death by anesthetics is in most cases due to asphyxia. But this, except with the most ignorant administration, is not due primarily to a want of air, but to paralysis of the respiratory center.

Circulation.—The phenomena observed on the **pulse** are usually *quickening in the first and second stage*, mainly from the increased movement, but partly from direct depression of the vagus center. There may, however, be temporary slowing or even stoppage from reflex irritation of the vagus through the trigeminus endings. The excised heart shows slowing from the start, through depression of the muscle. (Fig. 70. *C.*)

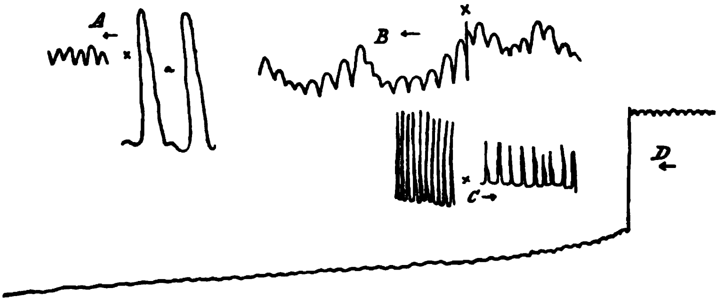

Fig. 70.—The action begins at ×; *A*, Cardiomyogram after ligature of aorta and vena cava: At *a* the heart has been under Digitalis; at X, chloroform water is injected; the beats are enormously weakened. *B*, Hypodermic injection of 5 c.c. of ether in anesthetized dog; it caused a fall of pressure. *C*, Cardiomyogram, excised heart (after Hedbom): Slowing and weakening (chloral). *D*, Shows death from chloroform, from vasomotor paralysis; the heart is not affected until very late.

The main effect is upon the strength rather than upon the rate. In the frog's heart the sinus and auricles are affected earlier and more strongly than the ventricle. The heart of the embryonic chick is primarily stimulated by ether. Chloroform depresses it from the start; later it causes an extreme dilatation. It is partly antagonized by ammonium.

In the *third stage* the pulse is soft and slow, but regular. The approach of the *fourth stage* is denoted by irregularity of the pulse with further weakening, due to depression of the cardiac muscle.

The **blood pressure** (Fig. 70, *B*), after a slight temporary rise, falls continuously almost from the start. The rise is due to reflex stimulation. The fall is due to a combination of paralysis of the heart muscle (Fig. 70, *A* and *C*) and vasomotor center (Fig. 70, *D*). The former may be demonstrated on the isolated heart, whilst the latter is shown by the fact that, even with the lowered blood pressure, the outflow from the mesenteric vein is increased, and reflex stimulation of the vasomotor center is no longer effective. It seems that the paralysis of the heart does not become serious until much later than that of the vasomotor center.

Pupils.—These are dilated during the *first and second stages*, as the ordinary result of excitement. During the *anesthesia* they are strongly constricted, due to depression of the dilator center. In the *fourth stage* (asphyxia) stimulation of the center causes dilatation. Dilatation also occurs in *recovery*. The danger-sign, therefore, is dilatation of the pupils, unless this accompanies evidence that the patient is coming out of the influence.

III. CAUSES OF DEATH UNDER ANESTHESIA.

In the later stages of the anesthesia this usually results from *medullary paralysis*, aided by direct paralysis of the heart muscle, and, as has been pointed out, the respiration normally gives out before the other centers or the heart. But it must not be forgotten that the latter are also weakened, and would eventually lead to death even were the respiration kept up. The respiration is simply the weakest link in an interlocking chain, and when another link is abnormally weak, it may give out first. In cases in which the heart is not normal, this may and does give out before the respiration.

But in another class of fatal cases, especially with chloroform, the course of events may be entirely different:

Here the heart stops suddenly, often when only a few whiffs of the anesthetic have been taken. This is especially apt to occur when the patient has been struggling or holding the breath. The chloroform is forced tighter upon him, and when a respiration is taken, the vapor is inhaled in almost undiluted form. Now, the concentration, and not the total quantity, of the anesthetic constitutes the primary element of danger. This concentrated anesthetic vapor may produce sudden stoppage of the heart in two ways:

1. By reflex stimulation of the vagus through the trigeminus endings. This, though very alarming, is not usually dangerous with normal individuals, for stimulation of the vagus cannot stop the heart sufficiently long to consti-

tute an element of danger. In fact, this is a safeguard, in not allowing the concentrated anesthetic to be carried to the heart. But with a weak heart and depressed circulation this temporary stoppage may turn the scale. This vagus stoppage does not occur when the anesthesia is well advanced, since all reflexes are diminished at this time. Besides, anesthesia causes a lowering of the irritability of the vagus endings in the heart.

2. The vapor is carried by the blood in very concentrated form to the heart, which it paralyzes through its direct action on the muscle. This is almost invariably fatal. Concentrated vapor, then, generally paralyzes the heart, whilst diluted vapor paralyzes the respiration.

Another cause of unpleasant symptoms of an irritant character lies in the *impurities* resulting not only from imperfect manufacture, but from the decomposition of the pure product. This decomposition is especially frequent with chloroform, resulting in the formation of Phosgen gas and of free Cl and HCl, all very irritant.

$$4CHCl_3 + 3O_2 = \underset{\text{Phosgen}}{4COCl_2} + 2H_2O + 2Cl.$$

$$COCl_2 + H_2O = CO_2 + 2HCl.$$

As this is greatly favored by exposure to light, chloroform should be kept in small dark-colored bottles. The addition of 1% of alcohol greatly retards this decomposition, but when chloroform is used with artificial light, the combustion of its vapor necessarily results in these products. It would, therefore, be advisable to use incandescent electric light, which, in the case of ether, would also obviate the danger of ignition.

Of course, many deaths during anesthesia are due to the inexperience of the anesthetizer, some possibly to impurities ; a few are undoubtedly unavoidable. But it is incorrect to attribute every death upon the operating table to the effects of the anesthetic ; for patients died upon the table when anesthetics were yet unknown.

One such case was of considerable importance in the history of anesthesia. When Simpson was about to try chloroform on a patient for the first time, the orderly who was carrying the bottle fell and spilled the chloroform. No other being obtainable Simpson proceeded to the operation, which was for hernia, without anesthesia. The patient died with the first cut. Had the chloroform been given in this case and the same accident had happened, its introduction into practice would have suffered a long delay. Other similar cases are not uncommon : A patient was to be operated and demanded chloroform. His condition, however, was so low that the surgeon feared to grant his wish, and to calm him held a cloth *without* chloroform before his face. Scarcely had the patient made four inhalations—of air—when he was dead. In preanesthetic days, the French surgeon Desault drew his fingernail over the perineum of a patient to mark the line of incision, when the patient suddenly gave a cry and was dead. And many similar cases of sudden death from the violent mental impression might be mentioned, besides deaths undoubtedly due to traumatic shock. Even at the present day patients often exhibit "psychic shock" when operated under local anesthesia, so that it is a general practice to precede this by morphin.

It is true that the public nowadays has largely lost that great fear for operations which formed the causes of the former cases, and that anesthetics lessen the danger of traumatic shock. But neither is excluded, and there is no doubt that many deaths attributed to anesthetics really have their cause elsewhere.

Besides these violent accidents occurring from the anesthetic at the time of its administration, it may cause less striking but equally dangerous **after-effects** and side-actions, depending upon the irritant action. A certain amount of *gastric irritation* is a constant phenomenon, but rarely assumes serious features. So is an irritation of the *respiratory* structures, which is further complicated by the inspiration of saliva and buccal bacteria, and may give rise to pneumonia. Previous disinfection of the mouth has therefore been recommended. Evidences of an *acute nephritis*—albuminuria and glycosuria, sometimes casts—are not uncommon, but may in some cases be referred to asphyxia. Chloroform causes the glycogen of the liver to be diminished, the sugar in the blood to be increased. Chloroform and ether have a marked action upon the *shed blood*, dissolving the red corpuscles and liberating the hemoglobin. It is not known whether they exert this action on the circulating blood when they are inhaled, but it may be that the *anemia and icterus* sometimes observed are due to this action. These after-effects are much more pronounced in the case of ether than of chloroform; for although, quantity for quantity, chloroform is by far the more irritant of the two, the absolute amount of ether taken more than balances this difference.

The cells of other organs of the body also suffer, especially with chloroform and when the anesthesia is prolonged.

The patient remains in a general apathetic condition and dies inside of several days with the general phenomena of heart failure. The autopsy in such cases reveals fatty degeneration throughout the body, and especially in the liver and heart. Recent researches make it appear that these fatty degenerations are not the dangerous element. They appear quite easily, but disappear again equally readily. The real danger seems to be in *degenerative changes in the cardiac ganglia.* These are cumulative and persistent. They are seen after chloroform, chloral, morphin, and large doses of atropin, but not after ether. They seem especially dangerous in the "status lymphaticus."

The *autopsy* in acute chloroform or ether deaths shows nothing beyond the ordinary phenomenon of death by asphyxia—heart distended, veins congested, etc.

In connection with anesthetics there is a question of some medicolegal importance—namely, whether anesthesia can be produced during sleep. Such cases are reported, but it must be extremely difficult, and consequently rare.

IV. CHOICE OF ANESTHETIC.

It must be considered as definitely settled that *chloroform is more dangerous than ether*. Statistics show that the immediate mortality is three to five times as great with the former.

In how far this is due to faulty administration does not enter into the question—there is as much inefficiency in the use of ether; and anesthetization cannot always be carried on by experts.

Granted, then, that chloroform is by far the more dangerous, it behooves to use ether except when this is specifically contraindicated.

The *contraindications to ether* arise principally from its more marked local irritant action. The patient himself usually prefers chloroform; and ether is contraindicated whenever there is a tendency to inflammation which might be exaggeratated by an anesthetic: bronchitis, nephritis, etc. *Chloroform*, on the other hand, is especially contraindicated where the circulatory apparatus is the seat of disease. It is also contraindicated in very long operations, on account of the late degenerations following it.

The principal *advantages of chloroform* arise from the quickness of its action, the small bulk required, its comparatively less volatility, and the fact that it cannot be ignited.

The *quickness of action* makes it indispensable where many operations must be performed in a short time, as on the battle-field. It is also a great advantage where talking and struggling are to be avoided. The latter may be very important in *atheroma or aneurysm*. On the other hand, ether is preferred with alcoholic "strugglers," to lessen the danger of sudden heart action. The *inflammability of ether* constitutes a serious objection to its use with artificial light or thermocautery. When used with the former, the lamp should always be adjusted above the patient, since the ether vapor is heavier than air.

All these rules may have to be discarded in the cases of certain patients which assert an *idiosyncrasy* against one or the other anesthetic.

Combination Methods.—In the attempt to combine the advantageous features of both anesthetics, it is often recommended to start the anesthesia with chloroform and continue with ether. This is necessary only in special cases, such as atheroma combined with heart disease, where the prolonged action of the chloroform and the primary struggling of the ether are both to be avoided; for ordinarily the danger of the chloroform lies precisely in the start, that of the ether in the course, of the anesthesia.

It has also been suggested to combine the anesthetics, as in the case of the "A. C. E. mixture." This consists of varying proportions of alcohol, chloroform, and ether, equal parts of each being a good combination.[1]

Such mixtures would probably present advantages over either anesthetic alone, if they were properly used. But perhaps even more experience is required to handle properly a mixture of this kind than to handle either of the others. Of other anesthetics of the hydrocarbon series, *bromoform* alone has been used to any extent, but it has never been popular, and its use is justly on the decrease. It is not very safe, decomposes very readily, and possesses no apparent advantages. *Ethyl bromid*, etc., have never attained any great popularity.

V. OTHER GENERAL ANESTHETICS ADAPTED TO ANIMALS.

The susceptibility of different animals to the various anesthetics is somewhat different from that of man; further, the question of expense is of some little importance, so that a separate discussion of this subject may be useful.

Chloroform, undiluted, is the most dangerous, and should generally be avoided in all cases. *Ether* is comparatively safe. So are *A. C. E. mixtures*. One composed of equal parts has given good satisfaction.

In the dog, these anesthetics are best preceded by a large dose of morphin (0.05 to 0.25 Gm. hypodermically, 4% solution) given half an hour before. This lessens struggling, and greatly diminishes the amount of anesthetic necessary. If the experiment admits, the trachea may be connected with a 2-necked Wolf's bottle containing the anesthetic. (See Chap. XXXIV.) The concentration of the vapor can be increased or diminished by lowering or raising the tube in the bottle.

The author has experimented to some extent with *gasoline* on dogs, and has obtained the same results as those of Elfstrand on pentan, pental, etc.

In frogs, the concentrated vapor of gasoline caused purely paralytic symptoms. In mammals, it is capable of being used when largely diluted (1 : 8 alcohol), and the anesthesia may then be kept up as long as two hours, without noticeable bad effects. If carefully handled, it produces no change in blood pressure, pulse, or respiration. It is, however, rather unsafe even in this concentration, since it produces its toxic effects very suddenly. However, when given in the *gasoline mixture* (Chap. XXXIV), it is no more dangerous and considerably more powerful than the A. C. E. mixture.

The toxic effects obtained from too concentrated gasoline vapor consist primarily in very characteristic convulsions. These are best seen when the gasoline is given in strong form without other anesthetic. The animal struggles violently, then falls on its side and claws the air with all fours, as if running. The pupils are widely dilated. Reflexes absent. The spasms are intermittent, and between them the dog is perfectly limp, except that the toes, tail, and eyelids continue to twitch. The respiration is first stimulated, then weakened. There is a paralysis of the vagus, then a depression of the cardiac muscle, and later of the vasomotor center. Either heart or respiration may stop first.

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[1] Billroth's mixture consists of: Chloroform, 3; Ether, Alcohol, āā 1.

(*Benzol* shows similar changes.)

Rabbits do not bear these stronger anesthetics very well, they are best anesthetized by the methods given in Chapter XXXIV.

Chloroform acetone (chloretone), which has been highly recommended by some (saturated solution by stomach, catheter 25 c.c. for rabbits, 250 c.c. for dog of medium size), has not been successful or safe in the hands of the author, proving even more dangerous than chloral. Other independent observers have also found that the fatal dose is one-seventh that of chloral, and that it lies much closer to the narcotic dose. Death results from respiratory paralysis, with simultaneous central vasomotor paralysis and cardiac depression—the latter, however, not as pronounced as in the case of chloral. There is also an effect upon metabolism, which finds expression in a great lowering of temperature and diminution of oxygen consumption, and the animal often shows marasmus when the acute effects have passed off.

Urethane also produces a marked fall of temperature, and in large doses a very profound and acute degeneration of the liver cells.

VI. PRACTICAL RULES FOR ANESTHESIA.

Preparations.—Before commencing the administration, the patient should be prepared by receiving a cathartic on the previous day, and nothing but a very light meal for at least two hours before the anesthesia, to prevent the discharge of the contents of the alimentary canal during the anesthesia. He should be carefully examined for cardiac, renal, and pulmonary disease. He should then be placed in such a position as to interfere to the smallest possible extent with respiration; the *head preferably low.* The clothing should be loosened and all foreign bodies—false teeth, etc.—removed from the mouth. All the instruments, etc., apt to be used should be at hand before the administration is started—both anesthetics, mask, hypodermic with strychnin, brandy, etc.

It is very useful to administer a hypodermic injection of Morphin $\frac{1}{6}$ grain and Atropin $\frac{}{200}$ about half an hour before the anesthetic is started. The former, besides its tendency to lessen the apprehension of the patient, lessens the struggling and excitement of the first and second stages, and thereby reduces the greatest element of danger; and, further, the amount of anesthetic required is much less—a great advantage in view of the after-effects. The atropin lessens the tendency to stoppage of heart and respiration, through vagus inhibition. It has also been proposed, with a view to the same result, to cocainize the nasal mucous membrane. The advantage of this seems very doubtful. Care should be taken to have the patient close his eyes.

In regard to the **administration of the anesthetic** itself: This is usually done by *inhalation*, since the amount can be much more readily regulated in that manner. Attention should be directed to the following points:

The *concentration of the vapor*. It must be well understood that the danger arises from the concentration of the anesthetic, and not from the actual amount employed. With regard to this concentration, experiments have shown that the percentage of ether in the respired air must be 3.6 vol.; of chloroform, 1 5 vol. These limits are quite safe, and such quantitative mixtures have, indeed, been given by special *apparatus*. Aside from the cumbersome nature of the latter, an important objection to such standard mixtures is the slowness with which they produce anesthesia. It is certain that much stronger mixtures than these may be borne for a short time, and are quite safe in starting the anesthetic. Nor have any of the other apparatus deserved or attained any popularity.

The fact is that no mechanical device can replace the sense of responsibility, the constant watchfulness, and the quick reasoning of the experienced anesthetizer. Anesthetization is not a physical experiment where the factors can all be foreseen, but the condition of the patient is apt to vary from moment to moment, and must be taken into account. The state of the respiration must be carefully watched: if the patient holds his breath, the mask must be held farther away, since the next respiration will be an especially deep one. When the respiration becomes slow and shallow, this signifies that a sufficient amount has been taken, and that the quantity may be lessened. The object is to give no more than is necessary to just keep the patient anesthetized. On the other hand, care must be taken to keep him thoroughly under the influence, for shock is much more common under partial anesthesia. Since the respiration and circulation react one upon the other, so that no change could occur in the latter without being noticed in the former, and since most accidents occur from stoppage of the respiration, it may be sufficient to watch this alone, as is advised by some. But as it is of the highest importance to discover beginning failure of the one or the other at the earliest possible moment, the anesthetizer cannot be considered as doing his duty unless he carefully observes both. The argument that watching the circulation distracts the attention from the respiration should not hold; the anesthetizer should be able to keep his attention fixed upon both.

The fact that the required concentration of ether is much greater than with chloroform, leads to the temptation not to admit sufficient air. This must be carefully guarded against, or asphyxial symptoms may result simply from a deficient supply of oxygen.

Chloroform is given on a cloth, held some little distance from the face, and best supported on a frame. With either anesthetic the mask should at first be kept fairly away from the mouth, until some narcotic effect is obtained, to lessen the feeling of choking from the concentrated vapor. The patient should be encouraged to breathe quietly and regularly. Counting is a good expedient for this purpose. With regard to the chloroform, this is best dropped in a regular manner on the cloth. The rate should under no circumstances exceed 60 per minute, and usually should not be over 12. After the anesthetic stage has been induced 6 drops per minute will usually suffice. This will be found better than to remove the mask altogether and reapply it with a larger dose when the patient shows signs of recovery.

The *tongue* may fall back and interfere with respiration, as denoted by noisy breathing. In this case it will usually suffice to push the jaw forward, but it may be necessary to draw out the tongue. If much *mucus* accumulates, this should be removed with a cloth. If *vomiting* occurs, the head should be turned to the side.

If the symptoms of the fourth stage (p. 439) should make their appearance, or if either heart or respiration should show signs of failing, the anesthetic should at once be withdrawn and restorative measures started. These consist in lowering the head of the patient, in order to give the medullary centers the benefit of any circulation still remaining. A few rhythmic compressions of the epigastrium may be tried, but if these do not succeed quickly, artificial respiration by any of the methods should be begun at once. The cardiac region should also be compressed at the rate of seventy times per minute, since this aids the action of the heart and supplies a mechanical stimulus. A venesection is sometimes efficient in starting the heart, but is always risky. *Faradization* of the phrenic and of the heart has also been advocated, but appears to be prompted more by the desire to do something than by any rational view of the object to be accomplished. Stimulation of the phrenic, to be sure, causes contraction of the diaphragm and inspiration, and if done intermittently, would take the place of artificial respiration. But it possesses no advantage over the latter, and besides the fact that the time required to adjust the apparatus might be much better utilized, there is apt to be stimulation of the vagus—a most undesirable feature.

With regard to faradization of the heart, there is no more effectual way known of killing this organ than electric stimulation (by the production of delirium cordis), and the only reason why more harm has not been done by this senseless procedure is that the electricity, as it is ordinarily applied, does not penetrate through the chest walls.

Of drugs, strychnin, by virtue of the stimulation of the respiratory and vasomotor centers, is very useful if given in time—*i. e.*, while it may still be absorbed. Injection of normal salt solution should always be tried.

One of the best methods of resuscitating animals is by strong sensory stimulation, as of the sciatic. Hypodermic injections of ether, which have been used in man, might be supposed to act in the same manner. But clinical observers condemn their use, and experiments on animals show that the stimulus is too weak to produce any effect (Fig. 70, *B*).

Small doses cause no perceptible change in blood pressure or heart rate, whilst larger doses produce narcosis with fall of blood pressure.

It is often necessary to keep patients lightly under the influence of an anesthetic when no skilled assistant is available, as in obstetric practice. Here a method of self-inhalation suggested by Brunton is very useful.

The inside of a tumbler is covered with blotting-paper. A few drops of chloroform are poured on, and this is given to the patient, with directions to hold it an inch from his mouth and inhale. This works automatically, for as the patient becomes narcotized he naturally allows his hand to drop, and so removes the tumbler; and as soon as he becomes conscious and sensitive to pain, he will replace it. It would not, of course, be possible to induce deep anesthesia in this manner.

Besides the use of anesthetics in operation, they are often used in *obstetrics*, especially chloroform. Not complete anesthesia, but merely a dulling of the pain, is desired here, and the dose should be small, since larger quantities are apt to prolong the labor. Small quantities are also used to dull the excitability of the central nervous system in strychnin-*poisoning* and other convulsions, as also in pain or insomnia.

Besides the narcotic action, the *local irritation* of these drugs is used therapeutically in the same manner as alcohol, chloroform being a very active rubefacient and much superior to ether, since the latter evaporates too quickly. The use of chloroform as anthelmintic and of ether for freezing is discussed elsewhere (Chap. XXX, F). Bromoform (1 to 7 drops on sugar) is given in whooping-cough.

VII. MATERIA MEDICA.

⁂ **Chloroformum** (U.S.P., B.P.).—Chloroform.—Contains at least 99% $CHCl_3$ made by distilling alcohol with chlorinated lime and purifying the product. Sp. Gr. 1.49. Soluble in 200 parts of water and in all proportions of alcohol or ether. Boiling-point, 60° to 61° C. Not inflammable. *Dose:* 0.1 to 1 c.c. (2 to 15 minims).

Preparations:

Aqua Chloroformi (U.S.P., B.P.).—A saturated solution in water. (Made by agitation.) Flavoring and hypnotic. *Dose:* 4 to 15 c.c. (1 to 4 drachms).

Emulsum Chloroformi (U.S.P.).—A 4% emulsion. *Dose:* same.

⁂ *Spiritus Chloroformi* (U.S.P., B.P.).—A 6% solution. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

⁂ *Linimentum Chloroformi.*—30% with soap liniment, U.S.P. [50% with camphor liniment, B.P.].

* *Mistura Chloroformi et Cannabis Indicæ Composita*, N.F.—Each teaspoonful contains 0.5 c.c. each Chloroform and Tr. Cannabis Indica; 0.25 c.c. Tr. Capsicum; and 0.01 Gm. Morphin Sulphate.

Tinctura Chloroformi et Morphinæ Composita (B.P.).—7.5% chloroform; 1% of Morphin Hydrochlor., and 5% of Dilute Hydrocyanic Acid; also Capsicum, Peppermint, and Cannabis Indica.

* *Bromoformum*, $CHBr_3$.—*Dose:* 0.05 to 0.4 c.c. (1 to 5 minims).

⁂ **Æther** (U.S.P.).—*Sulphuric Ether, Ethyl Oxid.*—Contains 96% by weight of $(C_2H_5)_2O$; made by acting on alcohol with strong sulphuric acid, distilling, and purifying the product. End-reaction $= 2C_2H_5OH + H_2SO_4 = (C_2H_5)_2O + H_2O + H_2SO_4$. Sp. Gr., 0.725 to 0.728; boils at 37° C. Inflammable. Soluble in 10 vol. of water.

This is the *Æther Purificatus* (B.P.). *Æther* (B.P.) is a less pure and more watery Ether.

Preparations:

⁂ *Spiritus Ætheris* (⅓ Ether, ⅔ Alcohol, U.S.P.) [$\frac{1}{10}$ Ether, $\frac{9}{10}$ Alcohol, B.P.].—*Dose:* 1 to 4 c.c. (¼ to 1 drachm).

Spiritus Ætheris Compositus (U.S.P., B.P.).—"Hoffmann's Anodyne."—Above with 2.5% of "Ethereal Oil." *Dose:* same.

Æther Aceticus (U.S.P., B.P.).—$C_2H_5.C_2H_3O_2$. Boiling-point, 76° C. Solubility in water: 8 parts.

Acetonum, $CH_3.CO.CH_3$.—Boiling-point, 56° to 58° C. Solvent for fats, resins, rubber, camphor, gun-cotton, etc.

* Not official.
The most important preparations are marked ⁂.

(D) GROUP OF HYDROCARBON HYPNOTICS.

All the members of the Hydrocarbon Group tend, in small doses, to produce sleep. But many have properties which prevent their being used for this purpose. Thus, chloroform and ether are too irritant to the stomach and later to other organs; and being rapidly absorbed and excreted, their action is not sufficiently lasting. Further, the preceding stimulation is not desirable.

1. The **hypnotic qualities of alcohol** have already been discussed, and its advantages will again be summarized on page 456.

2. Of the drugs belonging particularly to this group the oldest and most important is **chloral hydrate.**

This is chemically trichloraldehyd:

$$\underset{=\text{ Ethyl Aldehyd}}{CH_3.COH} \qquad \underset{=\text{ Chloral.}}{CCl_3.COH} \qquad \underset{=\text{ Chloral Hydrate.}}{CCl_3.COH.H_2O}$$

This substance was discovered by Liebig in 1831 and introduced as a hypnotic by Liebreich in 1869. He assumed that it was decomposed in the organism, as it is by the action of alkalies in the test-tube:

$$\underset{\text{Chloral.}}{CCl_3.COH} + KOH = \underset{\text{Chloroform.}}{CHCl_3} + \underset{\text{Pot. Formate.}}{KCO_2H}$$

This is not the case, the chloral being excreted for the most part as urochloralic acid. This latter reduces Fehling's solution, which gave rise to the erroneous assertion that chloral causes glycosuria.

Action.—This occurs along the same lines as with the whole hydrocarbon series: *depression*, first of the brain, then of the spinal cord, and lastly of the medulla; and, finally, a direct action upon the heart muscle. The action is developed much more slowly, however, than with the fluid members of the series. With **small doses** it is quite possible to confine it purely to the brain, resulting in a lessened receptivity, and a lowering of the mental activity, and in this way producing sleep—for the most part indirectly by the cutting-off of afferent impulses. This resembles the *natural sleep* in every particular—as in the latter, the respiration and pulse are slowed, but not more than with normal sleep.

Somewhat larger doses cause a deeper sleep, with lessening of the spinal reflexes; and as the dose is increased, the depression of the medulla makes itself felt by *slowing of the respiration* and *fall of blood pressure.* The vasomotor paralysis is so prominent that chloral is often used in the laboratory to secure paralysis of this center. The pulse is also slowed through a direct action on the cardiac muscle. The action on the *isolated heart* is precisely as with chloroform: a lessened rate and amplitude, sometimes preceded by a short increase due to direct irritation. As in the case of chloroform, it is impossible to state to what extent the vasomotor and the cardiac paralysis respectively are concerned in the fall of blood pressure. A *dilatation of the cutaneous* vessels is quite a marked feature and may lead to the appearance of skin eruptions. Larger doses always cause a marked *fall of temperature* on account of this cutaneous vasodilatation coupled with the diminished production of heat from lessened movement (and perhaps lessened irritability of the heat-regulating centers ?). In *fatal doses* death is ordinarily caused by paralysis of the respiratory center, although it may take place by paralysis of a weakened heart, just as in the case of chloroform. On this account, and because it is apt to induce the same degeneration of organs, it is contraindicated in the same conditions as chloroform—degeneration of heart or vessels, nephritis, etc. ; also in lowered activity of the respiratory center.

The action of chloral upon *metabolism* consists in an increased destruction of proteids, the waste products being excreted in a less completely oxidized condition than is the case normally.

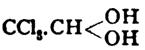
The *local action* of chloral is so pronounced as to allow of its use as a rubefacient. Its action on the stomach is consequently very prominent, and it must be largely diluted with water before administration ; else it may produce vomiting. In any case, large doses are apt to show after-effects, referable to a gastritis.

Chronic chloralism is a condition of no great rarity. It produces the same degenerations, moral and physical, as does alcohol.

The readiness with which the hypnotic action of chloral passes into paralysis of medulla and heart has instigated a search for substitutes, none of which, however, have so far succeeded in displacing the chloral entirely.

3. **Butyl chloral** is said to be specific in neuralgia of the fifth nerve.

4. **Chloral formamid :**



$\mathrm{CCl_3.CH}{<}\begin{matrix}\mathrm{OH}\\ \mathrm{OH}\end{matrix}$

Chloral Hydrate

$\mathrm{CCl_3.CH}{<}\begin{matrix}\mathrm{OH}\\ \mathrm{NH_2}\end{matrix}$

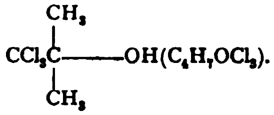
Chloralamid

$\mathrm{CCl_3CH}{<}\begin{matrix}\mathrm{OH}\\ \mathrm{NH.HCO}\end{matrix}$

Chloral formamid

has approximately the same action as chloral.

5. **Chloroform Acetone** (Chloretone) has recently been introduced. It has the formula :



$$CCl_3\overset{CH_3}{\underset{CH_3}{C}}\text{———}OH(C_4H_7OCl_3).$$

In the doses in which it is used it has no action on circulation or respiration, and is not dangerous in even much larger doses. But its effect is also not so very strong. Really narcotic doses are even more dangerous than chloral (see p. 446).

6. Chloralose is a compound of chloral and glucose:

$$\underset{\text{Chloral}}{CCl_3COH} + \underset{\text{Glucose}}{C_6H_{12}O_6} = \underset{\text{Chloralose}}{C_8H_{11}Cl_3O_6} + H_2O.$$

It differs considerably in its action from chloral. Besides being a stronger hypnotic, it heightens the reflexes, instead of depressing them, as does chloral. It also has a much lesser action on the heart, and produces practically no local irritation. It is somewhat more slowly absorbed. It deserves preference over chloral, except when the insomnia is due to an exaggerated reflex irritability. Others claim that its action is very uncertain.

7. **Hypnal** is a compound of chloral and antipyrin, and combines the actions of both.

Somnal is not a chemic compound, but a mixture of chloral, alcohol, and urethane.

Besides these narcotics in which the substituted Cl plays an important rôle, a number of Cl-free hydrocarbons are used. They possess less dangerous action on the medulla, but are also much weaker. Of these, one of the most typical is:

8. **Urethane,** $NH_2—CO—O-C_2H_5$. It is a very good and harmless hypnotic, but not very strong, and patients soon become immune to it. Urethane is very soluble and may be administered in solution, in doses up to ʒj.

It has quite a decided diuretic action. It lowers the excretion of nitrogen and sulphur, even in doses as small as $\frac{1}{3}$ Gm., whilst the phosphorus is increased.

9. **Hedonal** is methyl-propyl-carbinol-urethane, $NH_2—CO—OCH—CH_3.C_3H_7$. This new hypnotic is claimed to be as harmless as urethane in its action on the blood pressure and respiration, and yet twice as strong as chloral in hypnotic power. It is also markedly diuretic, and is therefore administered dry or with but little liquid. The hypnosis begins in about half an hour after the administration, and resembles natural sleep, the patient awaking refreshed. It is no so active as chloral in pain.

10. Sulfonal, Trional, and Tetronal.

$(CH_3)_2C(SO_2.C_2H_5)_2$ = Sulfonal.
$CH_3.C_2H_5.C(SO_2.C_2H_5)_2$ = Trional.
$(C_2H_5)_2C.(SO_2C_2H_5)_2$ = Tetronal.

These three resemble each other very closely in their action. Since Trional is the more soluble, more quickly absorbed, and more active, it is now preferred.

They are less dangerous than chloral, but do not act as strongly on pain, and if used for the latter, must be supplemented by Morphin.

Their excretion seems to be slower than their absorption, so that there is a tendency to a cumulative action. This leads to gastritis, renal disease, and ill-understood changes in the blood resulting in hematoporphyrinuria. The latter has so far been produced only in man and in rabbits. These phenomena can be avoided by intermitting the administration at times.

Sulphonal habit has been reported.

Quite a number of fatal cases of acute *sulphonal poisoning* are on record. The prominent symptoms were: Various forms of paralysis, often of wide extent—rarely spasms; various cutaneous eruptions; gastro-intestinal disturbance and extreme constipation; cardiac and respiratory weakness with a peculiar dyspnea; somnolence or insomnia, frequently with mental disorder. Hematoporphyrinuria is not always seen in acute cases. The autopsy is generally negative.

11. **Paraldehyd,** $3(CH_3CHO)$, is a safe and efficient hypnotic, the main objection to it lying in the disagreeable and very persistent taste, and especially odor. The latter is very lasting, since the drug is excreted in large part through the lungs. It is also irritant to the alimentary canal, and is contraindicated in gastritis.

12. **Amylene hydrate** is also sometimes used as a hypnotic. It has very pronounced after-effects like those of alcohol. It is claimed that it also diminished the polyuria and polydipsia of diabetes insipidus.

MATERIA MEDICA.

⁂ *Chloral* (U.S.P.) [Chloral Hydras, B.P.] (*Chloral Hydrate*).—Prepared by acting on alcohol with chlorin and purifying the product. Colorless crystals, freely soluble in water, alcohol, and ether. *Dose:* 0.3 to 1.5 Gm. (5 to 25 grains) (maximal dose, 3 Gm.). Largely diluted.

Syrupus Chloral (B.P.).—One drachm = 10 grains of chloral. *Dose:* ½ to 2 drachms.

**Chloralum Camphoratum*, N.F.—A liquid composed of equal parts of camphor and chloral. For external use.

**Mistura Chlorali et Potassii Bromidi*, N.F.—Each teaspoonful contains 1 Gm. (15 grs.) each chloral and Pot. Bromid, and 8 mg. (⅛ grain) each of Ext. Cannabis Indica and Ext. Hyoscyamus.

Butyl Chloral Hydrate (B.P.) (*Croton Chloral Hydrate*).—Soluble in 50 parts of water, freely in alcohol or glycerin. _Dose:_ 0.3 to 1 Gm. (5 to 15 grains).

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* Not official.
The most important preparations are marked ⁂.

*_Chloral Formamidatum_ (_Chloralamid_).—Soluble in 20 parts water or 1.5 alcohol. _Dose:_ 0.6 to 2 Gm. (10 to 30 grains); maximal, 4 Gm.

*_Chloroform Acetone_ (Chloretone).—Soluble in 125 water. Best given in capsules or tablets. _Dose:_ to 1 Gm. (15 grains).

⁂_Chloralose._—Freely soluble in hot water. _Dose:_ 0.3 to 0.5 Gm. (5 to 8 grains). Best in capsules.

*_Hypnal_ (Chloral Antipyrin).—Soluble in 6 parts water. _Dose:_ 1 Gm. (15 grains).

*_Urethane._—Soluble in 1 part of water. _Dose:_ to 4 Gm. (to 1 drachm). Best in small quantity of water.

⁂ _Hedonal._—Very soluble. _Dose:_ to 2 Gm. (30 grains). Best in powder or small quantity of spirits.

Sulfonal (B P.), ⁂ _Trional_, and *_Tetronal._—Soluble in 300 to 500 parts of water, readily in alcohol. _Dose:_ to 2 Gm. (30 grs.). Best as powders.

Paraldehydum (U.S.P., B.P.).—Soluble in 8.5 parts of water. _Dose:_ 1 Gm. (15 drops) dissolved in brandy.

*_Amylene Hydrate._—Soluble in 8 parts of water, readily in alcohol, etc. _Dose:_ 1 to 2 Gm. (15 to 30 grains). Best in glycerin.

It will be useful to sum up at this point all the remedies used for the production of sleep. They have received the name

HYPNOTICS.

(_Synonyms.—Soporifics_, _Somnifacients_; _Narcotics_, if they produce depression of the psychic areas aside from their soporific effect; _Anodynes or Analgesics_, if they are especially active in relieving pain.)

The **indication** for the use of Hypnotics is _insomnia_, whether from excitement, pain, cough, nervousness, etc.

In the treatment of this condition it must be remembered that the drugs of this class act purely symptomatically; that they soon lose their effect; that none of them are entirely free from objection, be it through the tendency to the formation of drug-habit, through an irritant effect, or through the danger of overdosage. They should not, therefore, be resorted to except in case of necessity. The dose at the beginning should be very small—it must be remembered that in many cases the action of the hypnotic itself need not be very lasting, for sleep once induced tends of itself to continue. And this small dosage presents the opportunity of enlarging the dose when the patient becomes accustomed to it. When the hypnotics need to be continued for a long time, it is well to change frequently to a hypnotic of another type, to return to the first later. This obviates to a great extent the irritant effects and also the difficulty of the patient becoming accustomed to the drug.

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* Not official.

The most important preparations are marked ⁂.

It is the duty of the physician to inquire into the underlying condition; the removal of this frequently renders drugs unnecessary. If it depend upon worry, caffein, late eating, late hours, or want of exercise, these conditions should be removed. When it depends upon a preconceived idea of the patient that he cannot go to sleep, then a harmless powder of any kind will often have the desired effect. Other cases are due to a faulty circulation: anemia of the brain is sure to induce sleepiness, while congestion is apt to result in insomnia. When the tone of the blood-vessels is impaired, the effect of gravity in lying down may send an added supply of blood to the brain, and in this manner produce wakefulness. Drugs like digitalis would be of the greatest benefit in such conditions. Much may be done by drawing blood from the brain by applying warmth to the extremities and abdomen.

The Hypnotics may be classed, according to their clinical action, into the following types:

1. *Alcohol*, including beer and wines: there is a tendency to preceding excitement, but no dangerous depression. The hypnotic action is weak.

2. *Urethane*, *Hedonal*, *Trional*, *Paraldehyd:* These have a comparatively slow but lasting action. They are only to a slight extent analgesic, and depress reflexes less than chloral; but, on the other hand, are less dangerous; they must be considered intermediate in strength of action and in danger between alcohol and chloral.

3. *Chloral* possesses a quick and lasting action. With large doses, it is markedly anodyne and lowers reflexes, but is dangerous on account of depression of medulla. It is apt to produce gastric irritation.

Chloralose differs from chloral in heightening reflexes, and it has less action on medulla.

4. *Aromatic Hypnotics.*—Lactophenin: The side-actions limit its value to febrile cases.

5. *Alkaloidal Narcotics:*

(*a*) *Morphin group:* Specifically against pain; heightens reflexes. Useful in cough.

(*b*) *Cannabis Indica:* Preceding excitement. Uncertain.

(*c*) *Hyoscyamin:* Especially in psychic exaltations and insanity.

6. *Mineral.*—Bromids (especially of potash): Supposed to act by simple depression of the activity of the brain-cells. No depression of medulla. Weak.

The drugs may also be grouped according to the form of insomnia in which they are especially indicated, as follows:

(*a*) In pain: *Morphin.* Large doses of *chloral* or *chloralose.*

(*b*) In *nervousness* or excitement or increased reflex irritability (tetanus, epilepsy): *Chloral, Trional.*

(*c*) In delirium or worry: *Hyoscyamin, chloral, bromids.*

(*d*) In mild cases: *Alcohol, Urethane.*

When several of these indications exist, much good may be done by the combination of several hypnotics.

Contraindications:

Morphin and chloralose: Increased reflex irritability.

Chloral: Depression of medullary centers. Tendency to vascular, heart, kidney, lung, or gastric disease.

Sulfonal: Tendency to nephritis.

CHAPTER XX.

(A) ASPHYXIANT GASES.

THIS series comprises a number of gases which agree with the hydrocarbon narcotics in their action, although differing widely in their composition.

(a) NITROUS OXID (LAUGHING GAS), N_2O.

As ordinarily used, the effects are largely those of *asphyxia*, differing from the ordinary asphyxia in that they are *less unpleasant* and lead less rapidly to heart standstill.

This asphyxia falls away, if the gas is inhaled mixed with oxygen (20% of the latter). In this case there is a direct action on the nerve-cells.

I. SUMMARY OF ACTIONS.

The effects consist in either case in a stimulation, followed by paralysis, of the central nervous system, beginning in the brain, then spreading to the spinal cord, and at last affecting the medulla. There is also a paralysis of the heart muscle, coming on in the last stages.

II. DETAILS OF ACTION.

The *symptoms* are at first those of *excitement*, usually of a pleasant variety (laughter, etc.). Then follow *loss of sensibility* to pain and incoordination of movements. This is as far as the action goes when the gas has been mixed with oxygen. If *pure gas* is used, or the mixture is used under pressure, these symptoms pass into those of **asphyxia**: loss of consciousness, heightened reflexes passing into convulsions, and later paralyses from the effect on the spinal cord. The effects upon the **medulla** lead, in the stimulant stage, to a *quickening of the respiration* and *stimulation of the vasomotor center*, with consequent high blood pressure. This latter is of some importance, since it is said to have given rise to *apoplexy* in persons predisposed to this. Later, both the respiratory and vasomotor centers are paralyzed as well as the heart muscle.

III. ORDINARY ANESTHESIA.

As ordinarily used, the gas is inhaled through a tightly fitting mask until the face becomes cyanotic, and is then removed. This anesthesia lasts thirty to sixty seconds—long enough for short operations, such as those of dentistry. Anesthesia cannot be kept up for any length of time by means of this gas, and its usefulness in surgery is therefore limited. It is the least dangerous of the anesthetics: of the many thousands of cases anesthetized with this gas, only about nine fatalities are recorded.

(b) CARBON MONOXID (CO).

(CARBONIC ACID, CO_2.)

Carbon Monoxid is the main poisonous constituent of the vapors arising from burning charcoal or coal, also of *illuminating gas*. This contains from 6% to 10%.

The *smell* of coal-gas is due to substances containing sulphur which have comparatively a small poisonous action, and are consequently *not a reliable index of its toxicity*. When breaks in underground gas-pipes exist, the gas may filter through the soil into dwellings. This filtration deprives it of its odor, but not of its toxic action, and it is therefore especially dangerous.

The *limit of toxicity* of carbon monoxid in air is five parts in ten thousand. It is fatal when it reaches 0.5% to 1%.

I. CARBONIC OXID HEMOGLOBIN.

The action of carbon monoxid is purely one of *asphyxia*. It combines with hemoglobin and so renders it incapable of carrying oxygen.

The *carbonic oxid hemoglobin* so formed is not a perfectly stable substance. Carbonic oxid combines with hemoglobin two hundred times more readily than does oxygen; consequently when oxygen is present in very great excess, the carbonic oxid hemoglobin will again be decomposed and oxyhemoglobin formed. It is in this way that persons quite deeply poisoned can be *resuscitated by artificial respiration*. On the other hand, it is not necessary that all the oxygen be displaced from the blood before death results.

The carbonic oxid hemoglobin possesses a *spectrum* very similar to that of oxyhemoglobin. It may be distinguished from this by the addition of some reducing agent, such as ammonium sulphid, which changes the two bands of oxyhemoglobin into the single band of reduced hemoglobin (see Fig. 71). The bands of carbonic oxid hemoglobin undergo no change.

The symptoms are probably purely asphyxial, and the description applies equally to **carbonic acid**, except that the action of the latter is much slower. When animals are placed in oxygen under a pressure of 2 atmospheres (to bring enough oxygen into solution in the serum), but containing sufficient CO to completely saturate their hemoglobin, they exhibit no symptoms, showing that the CO itself is not poisonous.

II. SUMMARY OF ACTIONS.

Stimulation, then paralysis of the central nervous system, the order being: brain, spinal cord, and medulla.

III. DETAILS OF ACTIONS.

The *first symptoms* are those of *excitement*, resembling very closely alcoholic intoxication. Then begin the symptoms referable to *stimulation of the medullary centers*. The *dilators of the cutaneous vessels* are first affected, resulting in flushing of the skin. This has a peculiar cherry-red color, due to the carbonic oxid hemoglobin. The *blood pressure* rises from stimulation of the vasomotor center. This is followed by paralysis, with marked fall of blood pressure. The extreme dilatation of the vessels gives rise to *ecchymoses*, which also show the peculiar cherry-red color, and when present are quite characteristic. The vasomotor paralysis is very slowly recovered from.

The *heart* is at *first slowed*, from stimulation of the vagus center, and the slowing is accompanied by *palpitation*. This is *followed by quickening* due to vagus paralysis. The *respiration* is *dyspneic*. Stoppage of respiration forms the usual *cause of death*. Of other symptoms referable to medullary stimulation, *vertigo*, *nausea and vomiting*, *and mydriasis* may be mentioned.

About the time of the medullary stimulation, the stimulation symptoms of the brain give place to paralysis of this organ. *Unconsciousness* occurs, as a rule, fairly suddenly. There is, of course, *anesthesia*. These conditions pass into *coma*. *Motor symptoms* do not usually occur until after the unconsciousness. They consist in *convulsions*, the seat of which has not been located, but which probably involve the whole central nervous system. These are followed by a *paralysis* beginning in the lower extremities and progressing upward. Stimulation of reflex spinal centers also results in the involuntary passage of feces, urine, and semen. The ratio of urea to total nitrogen, in the urine, is lessened in poisoning by coal-gas.

All these symptoms may be promptly removed—if the medullary paralysis has not advanced too far—by prompt and vigorous artificial respiration, which forms the **treatment** of such poisoning. The inhalation of oxygen gas is useful, if this be at hand.

The symptoms of inhaling *Carbonic Acid* are essentially the same as those detailed for CO. They occur even when the gas is mixed with a sufficiency of Oxygen. A closer analysis of the symptoms shows that the direct action of CO_2 on the nerve-centers is depressant. The primary stimulation is reflex, and arises through peripheral stimulation of afferent nerves of the respiratory passages. It occurs with any irritant gas. The action of CO_2 on the frog's heart causes a decrease in its rate and strength, and finally standstill.

The **after-effects** of carbonic oxid poisoning are quite lasting in man. This is probably *due, at least in part, to impurities*, for where the pure gas has been administered to animals, recovery was perfect, with no after-effects.

These late actions in man consist in a very *lasting headache*, due perhaps to the persistence of the *vasomotor paralysis*. *Nausea* is also quite frequent. The coma may persist considerably after all the carbonic oxid has been removed. On the part of the central nervous system there may be more or less persistent *paralysis* or *chorea*. A *loss of memory* is not infrequent.

Chronic poisoning by carbonic oxid or carbonic acid is found in persons living in impure air, and belongs properly to the subject of hygiene.

The *diagnosis* of coal-gas poisoning must be made by means of spectroscopic examination of the blood. For medicolegal purposes it must be remembered that carbon monoxid gradually disappears from the blood if it has been exposed to the air, probably inside of eight days.

As to the ultimate *fate* of CO in the organism, some experimenters claim that it is oxidized to CO_2; others, that it is excreted *in toto* unchanged. It is not possible to decide definitely between these at present, but the weight of the evidence is in favor of the latter view.

(c) CARBON DISULPHID.

This substance has only a toxicologic importance. Its extensive use in the arts in the vulcanizing of rubber, often carried on in small factories with very defective hygienic conditions, frequently leads to chronic intoxication. It is also used as an insecticide, and this has given rise to poisoning.

Acute poisoning is very rare. On animals the *symptoms* resemble those of *asphyxia*, although it is not known to what extent they are due to this, or to the direct action of the drug. They consist in convulsions, anesthesia, paralyses, and death by stoppage of respiration.

Symptoms of Chronic Poisoning.—These may not appear for weeks, months, or even longer. They consist in a depression of the central nervous system, preceded in some cases by a less well-marked excitation. They may be divided into three stages:

The *first stage* consists mainly in disturbances of the *sensorium* (headache, formication, vertigo, etc.), and also in *gastro-intestinal catarrh.*

The *second stage* shows *mental excitation*, sometimes passing into *mania.* There is at the same time a *diminution of muscular power.*

The *third stage* shows mainly *paralytic* symptoms. The *mental faculties* and the *special senses* are impaired. There are *tremors*, *contractures*, convulsions, or *epilepsy.* There are also *peripheral neurites*, leading to paralysis and atrophy of the muscles. These show the reaction of degeneration. *Ataxia* has also been reported.

For the rest, the symptoms are those of *marasmus.*

Death does not occur until very late.

The nerve-cells and dendrites show marked degenerative changes.

(d) ARSENIURETTED HYDROGEN (AsH_3).

Its action is different from that of arsenic. It produces a destruction of blood-corpuscles, and consequently anemia and icterus. For the rest, it causes nephritis and general asphyxial symptoms. It is impossible to say at present whether those asphyxial symptoms are due to the direct action of the drug on the respiratory center, or to the diminution of the blood-corpuscles.

(e) NITROBENZOL.

This substance also produces purely asphyxial symptoms (more closely resembling those of methemoglobin).

(B) OXYGEN.

This element exists in two forms: as Oxygen, O_2, and as O_3 (ozone).

Ozone (O_3).—The presence of this gas in the air is often claimed as one of the attractions of health resorts, but it exists at best in extremely small amounts (*e. g.*, 0.015 to 15.8 milligrams in 100 liters of air). These could not have any effect of whatever kind.

Effects of Inhalation.—Ozone has not so far been obtained pure, since all the methods used for its manufacture also develop nitrous acid. The gas produced in this manner is quite a strong local irritant, causing inflammation of the mucous membranes, etc. Smaller doses act rather as a narcotic, and later produce somnolence, convulsions, and finally death by edema of the lungs.

Oxygen.—In view of the necessity of oxygen to life, it has been extensively tried to utilize this gas in almost all diseases. However, it has not been as successful as its advocates had hoped. In explanation of this, and to establish the rôle of oxygen therapy, it must be remembered that the capacity of the blood for the absorption of oxygen is limited. It forms a definite chemic compound with hemoglobin, and as soon as the latter is saturated, the blood will not take up any further amount, no matter how great the percentage of oxygen in the atmosphere. Even less than the amount existing in the ordinary air seems quite sufficient to saturate the blood, if left in contact with it a sufficient length of time. With the normal amount of oxygen in the air, the normal rapidity of circulation, and the normal extent of the lung surface, the blood is almost, but not completely, saturated. This small difference between the possible and actual saturation seems sufficient to cause some stimulation to the formation of erythrocytes; so that the prolonged and repeated administration of oxygen raises the number of corpuscles and hemoglobin even in normal individuals, but the effect is certainly quite small in health.

The case is very different in disease. When the absorption of oxygen is in any way impeded,—by mechanical obstacles in the respiratory passages, as in croupous conditions; by the lessened amount of lung surface, as in pleurisy and emphysema, pneumonia, or edema; by a lessened amount of oxygen in the air, as in poisoning by asphyxiant gases,—the blood passes through the pulmonary circulation before it has time to absorb all the oxygen which it is capable of absorbing. Hence, in all these conditions oxygen would be indicated without question. Were it not for practical difficulties, the admixture of oxygen to the vapors of anesthetics would be the ideal way of administering these substances, since it very greatly lessens the danger of asphyxiation, without interfering with the anesthetizing effects.

More obscure and doubtful, however, are its benefits in conditions where the absorption of oxygen is not interfered with, but where oxygenation is none the less deficient: anemia, leucemia, chlorosis, fatty degeneration, etc. Oxygen causes an improvement in these cases. This is probably explained by the above-mentioned stimulating effect of the slight excess of oxygen saturation over the normal. The appetite is increased, the fat disappears, the red corpuscles and hemoglobin are increased in quantity. It is similarly useful in strychnin, etc., poisoning. (See p. 135.)

An important drawback to the use of oxygen in private practice is the difficulty of storing and transporting the gas. The quantity required is quite large; 30 to 40 liters at atmospheric pressure being the dose. However, it can be correspondingly lessened by using the compressed gas, which is conveniently stored in metal cylinders.

CHAPTER XXI.

(A) CAMPHOR GROUP.

I. MEMBERS.

Camphor and substances chemically allied to it—*i. e.*, camphoric acid, monobromated camphor, Borneo camphor, menthol, thymol, musk, etc.

Camphor is a stearoptene—*i. e.*, a solid body deposited from a volatile oil. Chemically it belongs to the terpenes, having for type turpentine, $C_{10}H_{16}$. This group may be split up, so that there are hemi-terpenes, C_5H_8, sesquiterpenes, $C_{15}H_{24}$, etc.

The bodies belonging to this group have the following composition:

$C_{10}H_{16}$ = Turpentine.
$C_{10}H_{16}O$ = Camphor $\left\{\begin{array}{l} C_{10}H_{15}BrO = \text{Monobromated Camphor.} \\ C_{10}H_{16}O_4 = \text{Camphoric Acid.} \end{array}\right.$
$C_{10}H_{18}O$ = Borneo Camphor.
$C_{10}H_{20}O$ = Menthol.

This group bears a *general resemblance to the essential oils* from which the members are derived.

Camphor is first mentioned in the Arabic literature about the sixth century. It was at this time very rare and valuable, and was not prepared artificially, as camphor is now, but was a kind found native in the trunk of a Sumatran tree.

The action is closely *related to the carbolic acid group.* The most important difference is on the central nervous system, in which this group brings out the stimulating phase, whereas with the carbolic acid group the paralysis is the more conspicuous. In this manner camphor is also related to the picrotoxin group.

II. SUMMARY OF ACTIONS.

1. Stimulation of the central nervous system, followed by paralysis in large doses.

The action on the central nervous system begins in the brain and then goes on to the medulla. In the frog the spinal cord is first involved and paralyzed, so as to hide any action on the brain.

2. Stimulation of the cardiac muscle.

3. Locally, stimulation and paralysis of the sensory nerve endings; also stimulation of the nerves conveying sense of cold in the case of menthol.

4. Mildly antiseptic, after the manner of essential oils.
5. A curare action on striped muscle.

III. DETAILS OF ACTION.

1. **Central Nervous System.**—(a) **Brain:** The stimulant symptoms begin in man with *impulsive movements*, confusion, *delirium;* then follows *unconsciousness* with *epileptiform convulsions.* The latter have been attributed to stimulation of the medulla, but some experiments seem to show that they are, at least partly, located in the brain. The lower animals give expression to this excitement by increased motion.

(b) **Stimulation of the medulla** is shown in man first by *vertigo;* later all the medullary centers are stimulated; the *respiration* is increased in volume and rate. The *blood pressure* rises; the *face and skin are flushed,* due to stimulation of the vasodilator center. *Large doses paralyze* the medulla and cause *death by collapse.* The (c) **spinal cord** also shows some *stimulation, and finally paralysis,* but this *does not come on until late,* and is not important *in mammals.*

(d) In **frogs,** on the other hand, the action on the spinal cord is *very pronounced,* and consists in a *paralysis.* This entirely obscures any action which the drug may have higher up in the nervous system in these animals. It appears that the path for reflex impulses is blocked before that for impulses coming from the higher brain.

(e) **Action on the Circulation:** The *blood pressure* usually *rises,* or shows alternate rise and fall.

That the rise in blood pressure is not due to any great extent to convulsions is shown by the fact that it occurs in curarized animals. It is caused mainly by a *stimulation of the vasomotor center;* and this stimulation must be *intermittent* in character, for the variations in the blood pressure are independent of the respiration. The *stimulation of the heart* also contributes to the rise of blood pressure, as is shown by the fact that this occurs even in deeply chloralized animals. The *reflexes,* especially those arising from the stomach, also contribute to it, as some rise is seen before any of the camphor can be absorbed.

2. The action on the **heart** consists, on the whole, in a *slowing,* but the contractions are, at the same time, greatly *strengthened.* Possibly this is due to some extent to stimulation of the medullary cardiac centers; but it is in greatest part due to a *direct stimulation of the cardiac muscle;*

for in the frog's heart the strengthening occurs here after any poison, showing that its action is mostly on the muscle-fibers themselves, and not upon any nervous mechanism. On the normal heart it produces lengthening of the systole and shortening of the diastole; somewhat after the manner of digitalis.

3. The **local action** is similar to that of the essential oils, or of very dilute carbolic acid, producing some *irritation and then anesthesia.* This determines its use for local application in liniments. **Menthol** shows a peculiar stimulation of the nerves conveying the sense of *cold.* The skin *feels* cooled after the application of the substance, although there is no fall in the temperature, the vessels in fact being dilated. The irritability of the endings for the sensation of heat is also increased.

The *irritant action* of small doses of camphor *on the digestive canal* is used *against dyspepsia.* Large doses produce *vomiting.*

4. Applied directly to frog's skeletal muscle, it produces a **curara-like action.** This is not seen in mammals.

5. Camphor has a slight **antiseptic action** which determines its use in mouth-*washes* and *gargles;* and it also forms a quite efficient *intestinal* antiseptic, the amount of combined sulphates in the urine being lessened by it.

IV. ABSORPTION.

On account of its volatility camphor is absorbed quite readily, although it is insoluble. However, the absorption presents very great variations, which make the action extremely uncertain, and greatly interfere with its usefulness in therapeutics.

The actions of the

V. OTHER MEMBERS OF THE SERIES

are so similar to those of camphor that the preceding description applies to them also. They have no advantage over camphor in therapeutics. *Musk* is supposed to act in the same way, but almost nothing is known about this substance.

VI. THERAPEUTICS.

1. The general action of camphor on the **central nervous system**—that is to say, the stimulation which it produces—

is made use of against all *collapse* conditions. The stimulation, as has been pointed out, is perhaps partly reflex. The *uncertain absorption* interferes very greatly with its usefulness. On the other hand, camphor has been used as a *nervous depressant*, as an *anaphrodisiac*, and so on. This rests on no rational basis.

It has also been employed against *hysteria*, but considering the uncertain course of this disease, it is impossible to say whether camphor is of any benefit.

2. **The dilatation of the cutaneous vessels** makes camphor useful as a **diaphoretic**, and in *colds*.

Like the other Terpenes, Camphor has found some employment in *tuberculosis*. The least objectionable method would seem to be give it as emulsion per rectum, about 1 Gm. per day. It has also been used subcutaneously, 0.01 Gm., dissolved in oil, being injected daily. Most observers report it as unsatisfactory.

3. Camphor is used for its **local action** on the skin as a *counterirritant*, and for its *local anesthetic* effects. For the latter, *menthol* in the form of menthol pencils is especially useful. Camphor itself is employed in the form of spirits of camphor or oil of camphor, often as an ingredient of liniments.

4. Its local effects upon the gastric and intestinal canal have caused its employment in **dyspepsia** and as a *carminative* and *intestinal antiseptic*. For this purpose, 0.3 Gm. is taken three times a day. Like the essential oils, it forms a frequent addition to *gargles and mouth-washes*.

VII. MATERIA MEDICA.

⁂ **Camphora** (U.S.P., B.P.).—*Camphor.* —A stearoptene obtained from *Cinnamomum Camphora*, Laurineæ; China and Japan.

The wood is distilled with water and the solid Camphor separates from the distillate. It is further purified by sublimation. Very sparingly soluble in water, freely in alcohol, etc., and in fixed and volatile oils. *Dose:* 0.2 to 1.2 Gm. (3 to 20 grains).

Preparations:

Aqua Camphoræ (U.S.P., B.P.).—A saturated aqueous solution; very little therapeutic action. *Dose:* ad libitum.

⁂ *Spiritus Camphoræ* (U.S.P., B.P.).—A 10% solution in alcohol; not miscible with water. The best form for internal administration. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

⁂ *Linimentum Camphoræ* (U.S.P., B.P.).—*Camphorated Oil.*—A 20% solution in Cottonseed Oil. Best form for external use.

The most important preparations are marked ⁂.

Linimentum Camphoræ Ammoniatum (B.P.).—Contains camphor, ammonia, alcohol, and oil of lavender.

Ceratum Camphoræ (U.S.P.).

Tinctura Camphoræ Comp.—(B.P.) (Paregoric).—See under Opium, page 222.

* *Camphor-Chloral* (N.F.).—Equal parts. Used externally.

Camphor is also contained in the following pharmacopœial preparations: Linimentum Belladonnæ; Linim. Sinapis Comp.; Tinct. Opii Camph.; Pulvis Morphinæ Comp.

* *Borneo* (*Sumatra*) *Camphor.*—From *Dryobalanops Camphora*, Dipterocarpeæ.

Camphora Monobromata (U.S.P.).—Made by heating Bromin and Camphor. Insoluble in water, soluble in alcohol. *Dose:* 0.12 to 0.6 Gm. (2 to 10 grains).

* *Acidum Camphoricum.*—Made by oxidizing Camphor with Nitric Acid. *Dose:* 0.6 to 2 Gm. (10 to 20 grains). Said to be specific in night-sweats of phthisis. Two Gm. are given two hours before the expected sweat. Externally: As a mild antiseptic gargle, wash, and injection in the manner of Camphor, over which it has the advantage that it can be dissolved in any proportion by adding 10% of alcohol for each % of camphoric acid. It is usually employed in strengths of from 0.5% to 6%.

* *Agaricin*, from *Boletus Laricis* (*Dose:* 0.005 to 0.03 Gm), is also used in these night-sweats. Large doses paralyze the heart and respiration.

⁂ *Menthol* (U.S.P., B.P.).—Stearoptene derived from the volatile oil of various species of Mentha. Slightly soluble in water, freely in alcohol. *Dose:* 0.03 to 0.12 Gm. (½ to 2 grains). *Emplastrum Menthol* (B.P.).—25%.

⁂ *Thymol* (U.S.P., B.P.).—Stearoptene (Phenol) from Thymus vulgaris or Carum ajowan. Uses similar to camphor, but more pronouncedly antiseptic. *Dose:* 0.05 to 1.0 Gm.

(B) HYDROCYANIC ACID GROUP.

I. OCCURRENCE.

Hydrocyanic acid exists as amygdalin in many plants. This amygdalin, when pure, is almost entirely harmless, except as it is decomposed in the body. But in most plants it coexists with the ferment emulsin, by which it is split up in the presence of water into hydrocyanic acid, glucose, and benzaldehyd:

$$C_{20}H_{27}NO_{11} + 2H_2O = 2C_6H_{12}O_6 + HCN + C_6H_5.CHO.$$

One gram of cherry kernels yields 1.7 mg. hydrocyanic acid; one gram bitter almond pulp yields 2.5 mg. hydrocyanic acid.

The hydrocyanic acid may be supposed to take its origin through the interaction of nitrates and alcohols; thus:

$$HNO_3 + C_2H_6O = HNO_2 + \underset{\text{Aldehyd.}}{C_2H_4O} + H_2O$$

$$HNO_2 + C_2H_4O = HCN + HCO_2H + H_2O.$$

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* Not official.

The most important preparations are marked ⁂.

Their significance is probably a chemic one, since they enter into the make-up of proteids. The complex proteid molecule contains aromatic nitrils amongst its constituents. These are almost devoid of poisonous action. The hypothesis has been advanced that the toxic properties which may be acquired by proteids are due to the decomposition of these compounds.

II. SUMMARY OF ACTIONS.

Hydrocyanic acid is a *violent protoplasmic poison*. It is toxic to all forms of life. It inhibits fermentation and putrefaction. It retards the growth of plants and the movement of animal cells. It diminishes nutrition by interfering with the reducing power of the tissues. In warm-blooded animals, however, all the symptoms arise from the central nervous system.

Cyanids agree entirely with hydrocyanic acid in their action. The metallic cyanids also exhibit the same action. The ferro- and ferri-cyanids and sulpho-cyanids however show practically no hydrocyanic acid action unless they are decomposed, as by acids.

Hydrocyanic acid also forms ethers (*nitrils*) with the alcohols. These possess the same action as KCN. The only difference lies in the rapidity of the action, and this, again, depends upon the rate with which the cyan-radicle is liberated.

III. DETAILS OF ACTION.

When given in doses small enough to permit of watching its action, this is seen to consist in a *fleeting stimulation of certain parts of the* **central nervous system,** *followed by depression* and paralysis. The action *begins in the medulla*. The vomiting, respiratory, vagus, pupil-dilator, and vasomotor centers are all stimulated. Then comes *unconsciousness*, and after this *convulsions*. In man these are probably mainly medullary in origin. Then follows paralysis of the whole central nervous system. Involuntary evacuations of feces, urine, and semen are frequent.

Death occurs by stoppage of respiration, the **heart** continuing to beat for a short time. Isolated twitchings of the cardiac muscle may be seen for a considerable time after the regular movements have ceased. These are of the same origin as the postmortem twitching seen in skeletal muscles, and are not sufficient to maintain any circulation. The action on the heart consists in a *paralysis of the automatic property:* a heart which has been stopped by hydrocyanic acid cannot be started by atropin, showing that the stoppage is not due to stimulation of the vagus; and since the heart can still respond to stimulation by single contractions, the muscle is not paralyzed, but only its rhythmic power.

This stoppage of the heart is the real element of danger, although the respiration is the first to give out; for respiratory paralysis can always be remedied by artificial respiration, whilst cardiac paralysis cannot be relieved.

Applied to the skin, hydrocyanic acid causes **local anesthesia** by paralysis of the sensory nerves.

IV. EXPLANATION OF THE ACTION.

The phenomena of the action of hydrocyanic acid on the central nervous system—the stimulation of the medullary centers, the convulsions, the vascular paralysis, etc.—bear a close resemblance to those of asphyxia; and probably asphyxia plays a very important part in the production of these phenomena. The latter cannot be attributed entirely to this asphyxia, however, since they may come on too quickly. The effects on lower organisms are precisely the same as may be produced by depriving them of oxygen. The *anti-ferment action* of the hydrocyanic acid interferes with the absorption of oxygen by the tissues, so that these undergo what might be termed an "internal asphyxia," in sight of abundant oxygen. The diminished

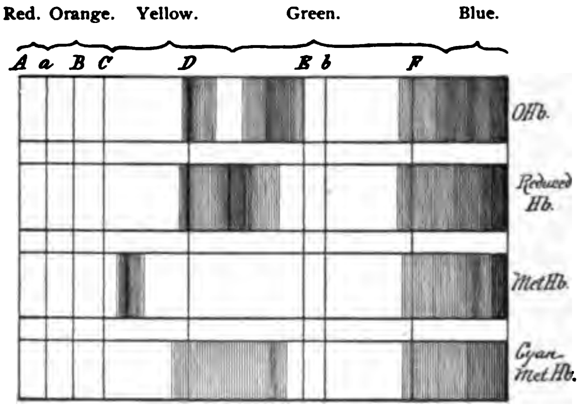

Fig. 71.—Spectroscopic band of blood pigments.

oxidation, therefore, resides in the tissues themselves, and not in the blood. The latter is also changed, hydrocyanic acid uniting with *hemoglobin*, but this combination is of a different nature from that with carbonic oxid, and has no influence upon the readiness with which oxygen is given off. When added to methemoglobin, it causes the formation of hydrocyanic acid methemoglobin, which differs from ordinary hemoglobin in its bright red color and in a peculiar band (Fig. 71). This hydrocyanic acid methemoglobin is responsible for the bright red ecchymotic spots seen after hydrocyanic poisoning. Methemoglobin can be used as a test for hydrocyanic acid.

Fate.—Hydrocyanic acid is very unstable; it changes very readily, even by mere exposure to light and air; and it undergoes still quicker decomposition in the body. Part of it combines with sulphur-containing molecules to form sulphocyanids. The fate of the remainder is unknown.

V. TOXICOLOGY.

Hydrocyanic acid is not very much used in criminal poisoning (0.5% of the recorded cases), because its quick action would soon lead to the detection of the crime. On the other hand, it or the cyanids form very favorite methods with suicides. Some cases are also reported of accidental poisoning by the gaseous acid.

This pure hydrocyanic acid, which is never seen outside of chemic laboratories, is extremely volatile and very toxic. The famous chemist Scheele, who discovered hydrocyanic acid, was killed by the vapors set free in the breaking of a flask of this fluid.

The strength of the commercial acid should, according to the pharmacopœia, be 2%. It is, however, quite uncertain, since decomposition is so rapid. On this depends the very varying time required for the onset of the symptoms.

This variability in the *appearance of the symptoms* is also due to differences in the absorption, according to whether the drug is taken on a full or on an empty stomach, a difference which is of especial importance in the case of hydrocyanic acid, since the drug is decomposed so rapidly that there is considerable chance of saving the patient when absorption goes on slowly.

The *fatal dose* is one to one and a half grains of HCN—not such a very small dose as the reputation of the drug would lead one to suppose. It obtained this reputation of high toxicity by its extremely rapid action. The shortest interval which has been noticed before the onset of the first symptoms may be stated as ten seconds. This is of considerable importance in medicolegal cases where the question may be what the patient could have done during these ten seconds. The *absorption* in any case is quite rapid. It can be absorbed even from the intact skin; and its application to raw surfaces has given rise to poisoning.

The *symptoms* consist in vertigo, mental dimness, headache, palpitation; then comes dyspnea, which may become very violent from stimulation of the respiratory center; the patient then becomes totally unconscious and shows very violent convulsions. During this stage the heart may be greatly quickened. The respiration becomes first difficult and then ceases. The heart at this time is very much weakened, but still continues to beat for a short time and then stops. In large doses all these symptoms may be wanting and general paralysis may come on at once, so that the patient may drop dead in a few seconds after taking the drug. There may or may not be convulsions in this case. If the patient lives for ten to fifteen minutes, the prognosis is good; not because the hydrocyanic acid has been eliminated in this short time, or because it has been destroyed, but simply because, if it has not killed, then the quantity has been so small as to be amenable to treatment.

The **treatment** consists ordinarily in evacuation of the stomach, which may also be rinsed with hydrogen peroxid. This substance can also be administered in the absence of lavage. It will destroy whatever of the poison is still in the alimentary canal. General stimulants, such as caffein, should be given. Artificial respiration should be maintained as long as the heart continues to beat.

Cobalt salts have proved effective in animals, forming cobalto-cyanids. But since this metal is itself toxic, its employment in man would be dangerous. Other metals give similar compounds, but are not nearly so effective.

Sodium Hyposulphite is theoretically a good antidote, since it forms the non-poisonous sulphocyanid, and is active even after the poison has been absorbed. It could be given hypodermically (100 to 500 c.c. of 3% solution). But so far it has not been tried on man.

The **diagnosis** *of cyanid-poisoning* may be made from the rapid course, since with most poisons the first symptoms occur only after some time. There are no *postmortem* changes except in the case of cyanid of potassium, which has a very marked alkaline reaction, and may therefore be caustic. Formerly great stress was laid upon the *blackness of the blood* in the internal organs. This is simply the result of the rapid death, the tissues being still alive after the stoppage of the circulation, and using up all the oxygen contained in the blood. It is, therefore, not at all characteristic of hydrocyanic acid, but occurs after any sudden death in well-nourished individuals. The *bright red ecchymotic spots* and the *odor* of hydrocyanic acid may be an aid. The proof of the substance must be done by chemic means, but in this case it is also necessary to determine the quantity present to avoid confusion with the accidental presence of the kernels of fruit, etc.

VI. THERAPEUTICS.

The *local anodyne action* is used against *itching of the skin* and pruritus, against *cough*, and against *vomiting*. If given internally, it must be in *small doses frequently repeated*, on account of the rapid decomposition. Hydrocyanic acid has also been given for other purposes, especially in *phthisis*, but this employment rests upon no rational basis; and, in fact, it is a question whether hydrocyanic acid is of any very great importance in therapeutics.

VII. MATERIA MEDICA.

⁂ **Acidum Hydrocyanicum Dilutum** (U.S.P., B.P.).—(*Prussic Acid.*) HCN. Should contain 2% of HCN. Made by decomposing Pot. Ferrocyanid with H_2SO_4, and distilling. Colorless liquid of characteristic odor. Very unstable; a black precipitate develops in time, and the strength decreases rapidly. Incompatible with metals. *Dose:* 0.06 to 0.2 c.c. (1 to 3 minims).

Potassii Cyanidum (U.S.P.).—KCN. Prepared by fusing Pot. Ferrocyanid with Pot. Carbonate and crystallizing. Soluble in water. *Dose:* 0.003 to 0.015 Gm. (1/20 to ¼ grain).

Drugs and Galenic Preparations containing HCN:

Prunus Serotina (Virginiana) (U.S.P.) [Prunus Virginianæ Cortex, B.P.]. *Wild Cherry.*—The bark; Rosaceæ; North America. Tannin; Amygdalin; Bitter glucosid.

Tinctura Pruni Virginianæ (B.P.).—10 c.c. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Extractum Pruni Virginianæ Fluidum (U.S.P.).—*Dose:* 2 to 4 c.c. (½ to 1 drachm).

Infusum Pruni Virg. (U.S.P.).—4 : 100. *Dose:* 60 c.c. (2 ozs.).

⁂ *Syrupus Pruni Virg.* (U.S.P., B.P.).—*Dose:* ad libitum.

Amygdala Amara (U.S.P., B.P.).—*Bitter Almond.*—The seed of *Prunus Amygdalus*, var. Amara, Rosaceæ; Mediterranean. Contains Amygdalin, fixed and volatile oil, etc.

The most important preparations are marked ⁂.

Aqua Amygdalæ Amaræ (U.S.P.).—*Dose:* 15 c.c. (½ oz.).

Oleum Amygdalæ Amaræ (U.S.P.).—The volatile oil. *Dose:* 0.01 to 0.03 c.c. (⅓ to ½ minim).

Spiritus Amygdalæ Amaræ (U.S.P.).—A 1% alcoholic solution of the oil. *Dose:* 0.6 to 3.0 c.c. (10 to 50 minims).

Laurocerasi Folia (B.P.).—Leaves of *Prunus Laurocerasus*, Rosaceæ.

Aqua Laurocerasi (B.P.).—Contains 0.1% HCN. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

(C) GROUP OF NITRITES.

This comprises all substances which either contain nitrous acid, or liberate it in the body—namely:

(*a*) nitrous esters: Amyli nitris.
Spir. Æther. nitros.
(*b*) nitroglycerin.
(*c*) inorganic nitrites.
(*d*) Hydroxylamin, NH_2OH.

I. SUMMARY OF ACTION.

1. Paralysis of the vasoconstrictor mechanism, both central and peripheral.
2. Paralysis of the vagus center.
3. Slow paralysis of muscle of all kinds with which they come into direct contact.
4. Methemoglobin formation.

1. Vasoconstrictor paralysis: This is first noticed in the skin of the face, in an area similar to that involved in blushing, but which may extend over the entire trunk to the ilium. The meningeal vessels undergo dilatation at the same time. There is consequently redness of the face, heat and throbbing in the head, and headache.

These first effects resemble very closely an incipient asphyxia. There is also some hyperpnea and cyanosis. The temptation might arise to refer them to the methemoglobin formation; but the spectroscope fails to reveal such at this time. It can also be shown on lower animals that the nitrite ion has a toxicity of its own, aside from the asphyxia. The latter, however, contributes considerably to the picture of the intoxication.

This flushing lasts but a very short time if the action of the drug be discontinued. At the same time the *heart is greatly quickened*, so much so that a rise of blood pressure is frequently observed at this stage, the dilatation being more than overcome by the quickened beat. The dilatation does not, however, remain confined to the skin, but spreads over the entire body, and relaxation of the splanchnic area in particular causes a speedy *fall of blood pressure* (Fig. 72) and a dicrotic pulse (Fig. 73).

A vasodilatation of this sort may result from a paralysis of the constrictor- or stimulation of the dilator-mechanism. The latter is excluded by the distribution of the areas involved. A constrictor-paralysis, again, may have its seat in the vasomotor center, in the peripheral nerve endings, or in the smooth muscle itself.

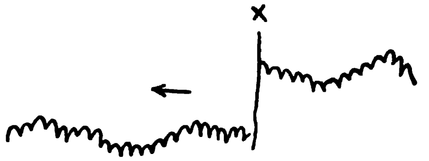

Fig. 72.—Nitroglycerin. Carotid pressure, dog. Action begins at ×.

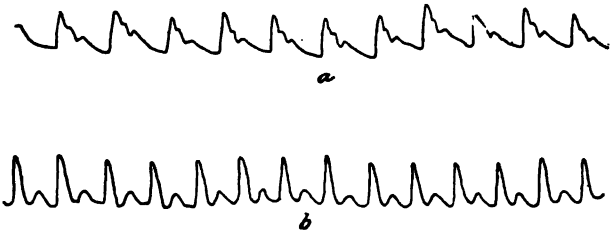

Fig. 73.—Amyl nitrite on sphygmogram: *a*, Normal; *b*, after inhalation of four drops.

Which of these is involved in the case of the nitrites has long been a subject of dispute amongst pharmacologists, and although it is not very important from a practical standpoint, it may be well to enter into the discussion somewhat more fully on account of its general bearing.

It must be considered as definitely settled that the nitrites produce a dilatation by acting upon peripheral structures, for they produce such dilatation in excised organs. This also shows that they act upon the muscle-fibers of the arterioles; for in excised organs the endings have been separated from their central connections, and therefore have already ceased to be active. In an animal in whom the maximal fall of blood pressure has been reached by a nitrite, stimulation of the splanchnic has still some effect, and this shows that the paralysis of the muscle is not complete.

It remains to be decided whether there is, in addition, a paralysis of the vasomotor center. This has in no case been demonstrated—but, on the other hand, there is no definite proof against it, for when there is a peripheral paralysis, no method at present known can demonstrate whether there is also a central paralysis, since central stimulation could not be transmitted. However, the quick manner in which the flushing of the face occurs and disappears suggests the probability of an early central action, later overshadowed by the peripheral effect.

2. The **tachycardia** is by far more pronounced in animals in which the vagus is intact and normally acting. It must, therefore, be attributed to a paralysis of the vagus center. However, nitrites may produce quickening in animals in which the vagi have been divided. In this case it may probably be explained by the lowered resistance, the heart, like any other muscle, contracting more quickly against a moderate than against a great resistance. No quickening is seen in the isolated mammalian heart.

Large doses of nitrites kill the *heart*, but this direct muscular depression is produced much less readily than in the case of the arterial muscle.

Another effect which may possibly be attributed to the central nervous system consists in a *quickening of the respiration*. But this is perhaps only secondary to the changes in the circulation and blood.

Similarly, the variations produced in the secretion of *urine* appear to be purely secondary, and will depend upon whether the renal arterioles or those of the general circulation are relatively more dilated; the former causing an increase, the latter a diminution, of urine.

Convulsions are also sometimes noted, but they also may be secondary to the asphyxia.

3. This **asphyxia** depends upon the production of methemoglobin. Nitrites differ from most other methemoglobin-formers in that the structure of the corpuscle is not destroyed. Consequently the only action is in lessening the readiness of oxidation, since methemoglobin parts with its oxygen much less readily than oxyhemoglobin. This may perhaps be responsible for the persistent glycosuria sometimes seen in animals. Methemoglobin, however, is not as stable a compound as is, for instance, CO; and when the tissues become actually O-starved, they can break up methemoglobin. It is consequently very difficult to kill animals in this manner, unless the nitrite be introduced

more rapidly than the methemoglobin can be decomposed —something which is never possible in man.

Regarding the practical

III. DIFFERENCES IN THE ACTIONS OF THE MEMBERS OF THE SERIES,

Amyl Nitrite, when taken by inhalation, produces a very rapid but also a very short action: it may be practically considered ended in twenty minutes. Nitroglycerin produces a much slower action, but this persists for several hours. The alkaline nitrites are decomposed by the HCl of the stomach with the liberation of free HNO_2, and consequently are quite irritant to this organ, and are little used.

IV. SUMMARY OF DRUGS CAUSING VASODILATATION.

The whole subject of Vasodilators may be grouped together in this chapter:

(These substances are called *Vascular stimulants* by the older authors, the "stimulant" referring to the system at large, not to the vessels. On account of the confusion to which the term leads, it should be entirely abandoned. The same authors usually speak of drugs producing vasoconstriction as "vascular tonics.")

1. Methods of Distinguishing a Vasodilatation.—A vasodilatation is the usual cause of a *fall in blood pressure.* But the latter may also be brought about by a weakened action of the heart. To distinguish, it is necessary to measure the venous *pressure simultaneously* with the arterial. A rise in the former will correspond to a fall in the latter if dilatation exists, whilst a weakened heart will cause a fall in both. Other methods are:

Direct inspection: the flushing of membranes or microscopic measurements in accessible situations.

Rise of temperature or *increase in volume,* the latter as measured by plethysmograph or oncograph.

Increased velocity (when the action of the heart is not simultaneously increased) as measured by the stromuhr or the circulation time (pigment or electric method).

Increased outflow under similar conditions.

2. Location of Action. — Theoretically, vasodilatation could be produced by paralysis of the vasoconstrictor mechanism or stimulation of the vasodilators; and vasoconstriction by the converse. But, with the exception of the cutaneous circulation, no drug has so far been found which acts upon the dilator mechanism without acting at the same time and more strongly upon the constrictors; and since the latter predominate so largely, the total result depends upon them.

The constriction mechanism might again be affected in *three places:* The center, the nerve endings, or the muscle-fibers. The methods of distinguishing a muscular paralysis have been sufficiently discussed on page 475.

If either the center or the endings are paralyzed, the drug will have no effect after section of the constrictor nerves. But if the center is the seat of the paralysis, stimulation of the peripheral stump will cause vasoconstriction; if the endings are the seat, it will have no effect. If the seat is in the center, this could be due to a direct action or to a reflex; the latter could be made out by excluding the corresponding afferent path.

Certain other drugs (*e. g.*, arsenic) produce a dilatation of the *capillaries* which might be confused with that of the arterioles.

3. The following are the **measures by which vasodilatation may be secured:**

1. Means which *increase the functional activity* of any organ increase reflexly the blood supply of that organ. The action of warmth, of counterirritants, of pilocarpin, etc., on the skin may be mentioned as examples.

2. *Drugs which act upon the center:*

(*a*) Those which depress the vasomotor center in common with the rest of the central nervous system—*i. e., Narcotics* (Chloral Group, Morphin, etc.).

(*b*) Those which act particularly upon the *thermoregulating center—i. e.*, Antipyretics.

(*c*) Those which act *particularly upon the vasomotor center*, Albumose and some toxins being the most typical.

(*d*) *Drugs which act upon the Ganglia:* Here belong Nicotin, Curare, Cocain, etc.

(*e*) *Drugs which act upon the Endings*, represented mainly by Atropin.

(*f*) *Drugs which act upon the Muscle*, the main action of the nitrites.

(*g*) *Drugs which act upon the Capillary Walls*, especially some of the metals (see Chap. XXVII).

V. THERAPEUTIC USES.

It will be noticed that most of these have other and more pronounced activities besides the general vasodilatation. They may come into consideration as diaphoretics, as diuretics, for the purpose of changing the distribution of blood, etc., and will be discussed elsewhere. But for producing general vasodilatation—and through it a fall of blood pressure and a lowering of the resistance to the work of the heart—the choice is restricted almost entirely to the nitrites. It has already been pointed out (p. 477) what differences exist amongst these.

The indications for such a general vasodilator action are the following:

1. *Excessive resistance* to the work of the heart (arteriosclerosis).
2. *Arterial spasms* (angina pectoris, some forms of migraine, asthma, cold extremities).
3. *Hemorrhage:* through lowering of general blood pressure.
4. In *toxic rise of blood pressure* (lead colic, barium, strychnin, digitalis).

VI. EXCESSIVE RESISTANCE TO THE WORK OF THE HEART.

This condition is shown by a high-tension pulse, with marked elastic oscillations but weak dicrotic wave.

A condition of this kind is dangerous mainly by reason of the extra work which it puts upon the heart. Such extra resistance is found especially in arteriosclerosis, also in *angina pectoris;* in *poisoning by* various drugs, such as Strychnin or Digitalis; and a relative excess exists when the heart itself is weakened, as in *fever*, whilst the pulse may indicate a normal or even low blood pressure.

When the rise of blood pressure is due to a nervous contracture of the vessels, as in angina or with strychnin, the nitrites are certain to give relief, and preference is given to amyl nitrite on account of its quicker action. But when the lumen of the vessels is greatly narrowed by fibrous thickening of their walls, and the muscle has largely disappeared, the nitrites naturally cease to be effective. Nitrites are therefore useless in angina pectoris if this is due to coronary sclerosis; and in *arteriosclerosis* they are for the same reason of use mainly in the early stages, and then they only give relief without curing the disorder. But this relief is so marked as to make them of great value. 0.6 mg. ($\frac{1}{100}$ gr.) of Nitroglycerin is given for this purpose three times a day, and the dose gradually increased until results are obtained.

When the resistance is not increased, but the heart is so weakened as to be unable to cope with it, as in fever, it must be remembered that these drugs cause a further lowering of blood pressure; and when this is already dangerously low, they would generally be contraindicated. But when this is not the case,—that is, when the weakening has not progressed very far,—a temporary relief may be secured, and this often suffices to restore the heart to its normal vigor. It would, of course, be advisable in all such cases to combine them with drugs which increase the power of the heart, such as digitalis; and, *per contra*, the addition of nitrites to digitalis is useful in preventing the vasoconstriction caused by the latter. Another condition which calls for the use of vasodilators is valvular disease, in cases in which the cardiac muscle is incapable of being stimulated to increased force by Digitalis—such as in fatty degeneration. In these Digitalis does harm instead of good, and nitrites are used as a last resort, effecting relief if they do not contribute to a cure.

Amyl nitrite has been found useful in certain obscure diseases: in epilepsy (especially when given at the time of the aura); in eclampsia; in hemicrania, etc. While it is often entirely without effect in epilepsy, it is of undoubted benefit in other cases, which are perhaps dependent on a vasomotor spasm of the vessels supplying the motor areas.

VII. MATERIA MEDICA.

⁂ *Amyl Nitris* (U.S.P., B.P.).—*Amyl Nitrite.*—$C_5H_{11}NO_2$. A colorless liquid of a peculiar odor, made by the action of nitric acid on amylic alcohol. Insoluble in water, miscible in all proportions with alcohol. *Dose:* 1 to 3 drops by inhalation from a handkerchief. It is best carried in the form of *pearls*—*i. e.*, small glass capsules, one of which is crushed in the handkerchief as needed.

⁂ *Spiritus Ætheris Nitrosi* (U.S.P., B.P.).—*Sweet Spirit of Nitre.*—An assayed alcoholic solution of Ethyl Nitrite ($C_2H_5NO_2$), made by acting on alcohol and sodium nitrite with sulphuric acid and distilling the product. Miscible with water or alcohol. *Dose:* 1.0 to 4.0 c.c. (¼ to 1 drachm).

Sodii Nitris (U.S.P., B.P.).—*Sodium Nitrite.*—$NaNO_2$. Soluble in 1.5 parts of water. *Dose:* 0.1 to 0.3 Gm. (2 to 5 grains).

⁂ *Spiritus Glonoini* (U.S.P.) [Liquor Trinitrini, B.P.].—*Spirit of Nitroglycerin.*—An alcoholic solution of 1% of Nitroglycerin (Trinitrin), $C_3H_5(OH)_3$. (Nitroglycerin is made by acting on glycerin with nitric and sulphuric

The most important preparations are marked ⁂.

acids.) *Dose:* 0.05 to 0.2 c.c. (1 to 3 drops). It is most conveniently given in *tablets*, each of which contains $\frac{1}{100}$ grain (0.0006 Gm.) of Trinitrin: *Tabellæ Trinitrini* (B.P.).

Nitroglycerin, although a nitrate, is readily converted into nitrites in the presence of alkalies, and this change takes place in the blood. Even the application of it to the skin causes some effect, and persons engaged in its manufacture suffer severely from headache during the first few days. After this, however, they appear to be quite unaffected, unless they leave work for several weeks and then resume the occupation. The work is said to be not unhealthful.

CHAPTER XXII.

(A) DIGITALIS GROUP.

I. MEMBERS.

THE digitalis group includes a very large number of drugs characterized by a peculiar action on the heart.

This action on the heart is so widely distributed that it must be regarded as a general phenomenon,—as the reaction of the heart muscle to certain changes in its environment,—and not as the specific action of any one poison or group of poisons.

It is a property which is common to a great many drugs, but is most conspicuous in the following substances:

1. $$\left.\begin{array}{l}\textit{Digitalein}\\ \textit{Digitalin}\\ \textit{Digitoxin}\\ \textit{Digitophyllin}\end{array}\right\}\text{Digitalis.}$$

Scillain (Urginea Scilla).
Adonidin (Adonis vernalis).
Oleandrin (Oleander).
Apocynin, Apocynein (Apocynum cannabinum).
Cheiranthin (Cheiranthus Cheiri).
Strophanthin (Strophanthus hispidus).
Helleborein (Helleborus niger).
Convallamarin (Convallaria majalis).
Euonymin (Euonymus atropurpureus).

Principles belonging to the Digitalis Group form the toxic agents of numerous arrow-poisons. Strophanthus species are used in this manner. Others are: The *Somali poison* (from Æscanthera Ouabaio, Apocyneæ; Ouabain); *Ipooh* (prepared in Malacca from the juice of Antiaris toxicaria; Antiarin).

In all these the active principle is a glucosid or resin.

2. The same action is found in a number of alkaloids;

most typically in *erythrophlein*, the alkaloid of sassy bark. (This alkaloid, however, also shows some of the reactions of glucosids.)

3. Quite a number of drugs belonging to other groups show a digitalis action on the heart: *Veratrin* in small doses; *Curin*; *Camphor*. Also a number of animal poisons, especially *Suprarenal* and *Pituitary* extracts; also a toxic principle derived from the toad's skin, *Phrynin*.

A digitalis action is often claimed for *Cactus grandiflorus*; experimental and clinical reports on this drug are as yet very contradictory.

4. Digitalis action is by no means confined to organic principles, but occurs with certain **mineral substances** in small doses; especially the *barium* salts and the free *hydrates* (containing the group OH); but even *normal salt solution* under certain conditions will exert a digitalis action.

While a digitalis action is a frequent phenomenon, it is much more strongly marked in some poisons than in others, and with the alkaloids it is largely obscured by other actions.

The digitalis group proper includes those of the above mentioned substances, whose active principle is a resin or glucosid, and erythrophlein.

The different members of the series agree very closely qualitatively, especially as far as the action on the heart is concerned, and may be well illustrated with the best-known member, digitalis. It is obtained from the leaves of the plant *Digitalis purpurea*, or fox-glove, in the second year of its growth. Other species of digitalis have similar actions. The only other member which has attained to any therapeutic importance is Strophanthus.

II. COMPOSITION OF DIGITALIS.

Digitalis seems to have been introduced into medicine comparatively recently. The first notice of its use is found about the middle of the sixteenth century.

The *composition* of digitalis is even now very imperfectly understood, and is still under discussion; but there seem to be at least five principles present in digitalis seed: Digitoxin, Digitalin, Digitalein, Digitonin, and Digitin (Schmiedeberg). These differ considerably in action and properties.

The first three, digitoxin, digitalin, and digitalein, have a typical digitalis action: a stimulation of the heart muscle and constriction of the peripheral vessels; whereas digitonin has a diametrically opposite effect, and acts as a depressant on the cardiac muscle and dilates the blood-vessels. Lastly, there is a principle, digitin, which is inactive.

The first two of these, digitoxin and digitalin, are insoluble in water when pure, but soluble in alcohol; whereas the second pair, digitalein and digitonin, are soluble in water. When the principles are mixed as they exist in the plant, the digitoxin and digitalin are taken up by water in suspension, through the aid of the digitonin, so that a 1 : 10 *infusion* contains two-thirds of the digitoxin of the leaf. (Digitonin belongs to the same group as the active principle of soap-bark, and it emulsifies the two resinous principles so that they can be extracted from the drug by water.) None the less, there are differences in the therapeutic effects of alcoholic and watery solutions:

The *alcoholic solution* contains mainly digitoxin, digitalin, and digitophyllin; whereas the aqueous solution contains, in addition, the digitonin, and a larger amount of digitalein, with a smaller amount of digitoxin and digitalin and digitophyllin.

Digitoxin is present in largest amount in the leaf; it is the strongest of the digitalis principles, and it is also the most irritant; it has a cumulative action. (The cumulative action is especially marked in those principles which are insoluble in water.) Digitalin has the same general action as digitoxin, but it is present in less amount and its action is weaker. Digitophyllin has also very similar actions. Digitalein is present in small amount; it is soluble in water, and its action is not cumulative. This is the least irritant of the principles, and has the least local action.

A similarly complicated composition exists with all the other drugs of the digitalis group. The active principle seems in no case to be single; and, furthermore, it is very apt to undergo decomposition.

Glucosids are always very unstable, and are easily split up. So are the members of the so-called sapotoxin and saponin group—the group to which digitonin belongs. The chemic composition of the whole series is obscure. The glucosids and resins seem to pass very readily the one into the other, and the composition of the drugs is not perfectly constant.

In the case of digitalis this decomposition leads to the formation of new resins; the digitoxin giving rise by decomposition to a principle, *toxiresin;* and digitalin and digitalein giving rise to the principle *digitaliresin.* These two resins, as also many of the undecomposed members of the group, have a picrotoxin action. The sapotoxins have a very marked local irritant action; so that, in addition to the cardiac digitalis action, which is the characteristic of the group, all these drugs show a certain amount of picrotoxin action—stimulation of the medulla—and of sapotoxin action—local irritation.

The decomposition products of digitalis, toxiresin, and digitaliresin, are present (if at all) in very small amount in the fresh plant, or in fresh preparations. They are formed, mainly by bacterial action, if the drug has been stored for a very long time under unsuitable conditions; for instance, in a moist state. They are formed in the same way in old infusions of digitalis. Their effect, as has been stated, is

TABLE OF DIGITALIS PRINCIPLES.

SCIENTIFIC NAME.	QUANTITY IN LEAF.	SOLUBILITY OF THE PURE PRINCIPLE IN WATER.	ACTION.	COMMERCIAL PRODUCTS (IMPURE). (The scientific products are designated "verum.")	DECOMPOSITION PRODUCTS. Schm. = Schmiedeberg. K. = Kiliani.
Digitalin, ...	Small or none.	Insoluble.	Cardiac stimulant and vasoconstrictor.	Digitalinamorphe Homocolle.	Digitoresin, Schm. Digitaligenin Digitalose } K.
Digitoxin, ...	Largest.	Insoluble.	Cardiac stimulant and vasoconstrictor.	Digitalin cryst. Nativelli. Digitalin purum amorph. French and Belgian. Digitalin chloroformique.	Toxiresin, Schm. Digitoxigenin Digitoxose } K.
Digitalein, ...	Small.	Soluble.	Cardiac stimulant and vasoconstrictor.		Digitaliresin, Schm.
Digitonin (amorphous and crystalline), . .	Small.	Soluble.	Cardiac depressant and vasodilator.	Digitalin purum pulv. German. = 50–60% digitonin. Digitalin cryst, Merck.	Digitogenin. Digitoresin, Digitonein, Paradigitogenin.
Digitin, ...	. . .	. . .	Inactive.		
Digitophyllin (only in leaves), ...	Small.	Insoluble.	Cardiac stimulant and vasoconstrictor.		
Digitoflavon (only in leaves), ...	. . .	. . .	Inactive.		

entirely different from digitalis, being a pure picrotoxin action, which is not at all desired in digitalis preparations. Their action is also much more toxic than the action of digitalis, so that an old infusion of digitalis, or a preparation made from spoiled specimens, is not only therapeutically useless, but has undesirable actions and presents danger, due to the presence of the toxic resins.

III. SUMMARY OF ACTIONS.

1. As the most important action, an increased irritability and contractility of the muscular fibers of the heart; followed by lessened relaxation; and, to a lesser degree, a constriction of the peripheral vessels by direct action upon their muscles.
2. A picrotoxin action—stimulation, and later paralysis, of the medullary centers.
3. A stimulation of the vagus apparatus in the heart itself.
4. A local irritant action, progressing to inflammation.

IV. DETAILS OF ACTIONS.

1. **Action upon the Heart.**—As this action is observed in the intact animal, it is composed of a number of features, and will have to be analyzed to be understood.

(A) One may begin with the **isolated atropinized frog's heart.** That is, a preparation in which the nervous elements have been as far as possible eliminated.

In a heart of this kind we observe, as a result of digitalis, first, a slowing through lengthened systole and lessened diastole. As the action progresses the systole becomes longer and stronger, and the diastole less and less, so that finally the heart remains tonically contracted, in in what might be called prolonged systolic contracture.

In this stage the contractions may be started again by forcibly distending the heart with liquid, and Schmiedeberg calls this stage one of increased "elasticity." "Contractility" would, perhaps, be more accurate.

During this stage rigor finally sets in and fixes the ventricles as a small white lump. This last degree of its action is reached first of all in the apex. Toward the end, the contractions assume somewhat of a peristaltic character. They begin at the auricle, spread to a slight extent over the ventricle, and then stop, so that the excursions are largest at the base of the heart and smallest at the apex. In this way the appearance of a peristaltic wave is produced. The auricles are not nearly as much affected as the ventricles; consequently the auricles may beat several times to every beat of the ventricle.

What effect will this action have upon the *work done by the heart?* Evidently it must cause a rise of pressure in the early stage, and a fall when the poisoning is more advanced. If the systole is increased, a rise of pressure will occur as long as the diastole is not too much lessened; but if the heart remains permanently in systole, the pressure will gradually grow less and less.

This action is *mainly upon the muscle-fibers* themselves, since it can be obtained from an apex preparation of the frog's heart, which is free from nerve ganglia, as also from the heart of the chick embryo. The explanation of it is similar to that of the veratrin action on skeletal muscle; namely, an increased tone of the muscle, an increased tendency to remain in a contracted condition, which, in the later stages in the frog's heart, becomes so great that the muscle finally does not relax at all, but remains contracted permanently until it goes into rigor.

The diagram (Fig. 74, *a*) gives the results following the action upon the muscle itself. Digitalis will produce a larger and more prolonged systole, whereas the diastolic excursion will be somewhat lessened and will not be at all lengthened in time. The total excursion therefore becomes less and less until the heart finally remains in systolic standstill. As long as the excursion is larger and the contraction of the heart stronger than is counterbalanced by the slowing, they will produce a rise of blood pressure; but when the systole becomes greatly prolonged, the blood pressure will fall.

(B) Action upon the Vagus.—This is stimulated both in the medulla and in the heart itself.

It will be well to study first what would be the effect upon the cardiac muscle and upon the heart's contraction of a *pure vagus stimulation.* Vagus stimulation slows and finally stops the heart, and it does so by prolonging the diastole. The phase, it will be seen, *is exactly the opposite of the digitalis action* upon the heart muscle; for in the latter the heart muscle is slowed by prolonging the systole and lessening the diastole, whereas the vagus action will slow the heart by prolonging the diastole and lessening the systole. The effect upon the blood pressure would be a fall from the very start of vagus action. (See Fig. 74, *b.*)

In the intact animal neither of these actions is seen in pure form after digitalis, but instead a combination of the two, which may produce different results. If both diastole and systole are increased, the result will be an increased work of the heart: the heart expanding and contracting further will throw out much more blood. At the same time, since the diastolic and systolic prolongation tend to counteract each other, the slowing is not as marked as with either action alone; consequently it is not strong enough to counteract the greater force, and as a result there is a progressive rise of blood pressure. (See Fig. 74, *c*.) This is the most typical result.

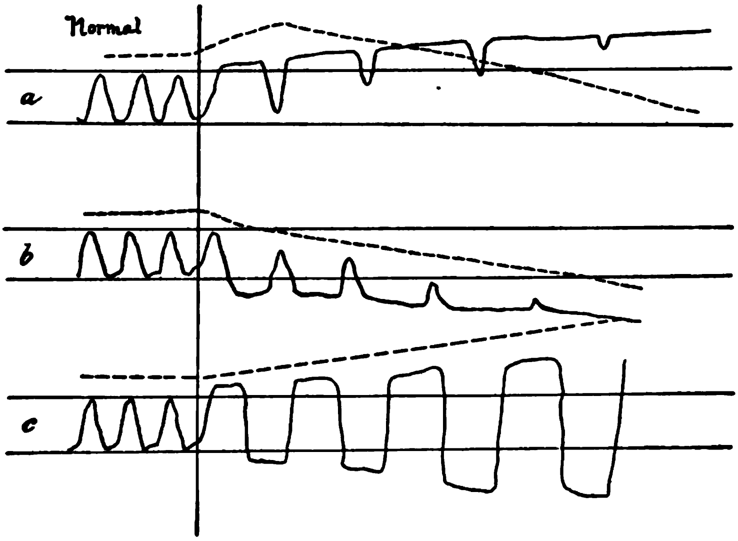

Fig. 74.—Diagram of digitalis action on frog's heart: *a*, On cardiac muscle; *b*, on inhibitory apparatus; *c*, one of the possible combinations. Solid lines, cardiac tracing (rise = systole); dotted lines, blood pressure.

The vagus and muscular actions may, however, appear in somewhat different order: one may come before the other. The typical muscular phase, the increased systole, may appear first; and when this has lasted for a time, it may pass off and give place to the vagus phase. Or the diastolic standstill may come before the muscular action, in which case the heart will first be slowed, with an increased diastole, and this be followed up by an increase of systole.

The action of digitalis on the vagus is not only central, but also peripheral. In the ordinary methods of application the muscular effect predominates over the peripheral vagus effect. But when the drug is *applied from the outside*, it reaches the nerve-filaments first, and causes a primary diastolic standstill; as

the poison penetrates, the muscular action comes to predominate, and the diastole gradually passes into a systolic condition.

These and other facts relating to the action of poisons have been mainly ascertained on the Williams Heart Apparatus, which may be described in this place.

Williams' Apparatus.—(Fig. 75.) This consists of a reservoir and a system of tubes provided with slit valves (*V* and *V'*) and a two-way cannula. These allow the perfusing liquid to get into the heart (*H*) and to be pumped in a definite direction. The cannula is introduced through the bulbus aortæ into the ventricle and tied. (The apex of the ventricle may be used alone.) Each contraction of the ventricle forces the blood through *V'* into the upright tube, and from here into the reservoir. The relaxation of the heart allows the liquid to enter from *V*. The auriculoventricular valves prevent the blood from flowing back into the auricle. The number of drops flowing into the reservoir can be counted, and give an idea of the work done. By raising or lowering the reservoir the intracardiac pressure can be varied; by applying the screw-clamp beyond *V'* one may introduce resistance; by clamping this tube altogether and opening communication to a small mercury manometer the absolute pressure can be measured and tracings taken. The changes in volume, corresponding to the extent of the excursions, may be read from the millimeter scale, *MS*.

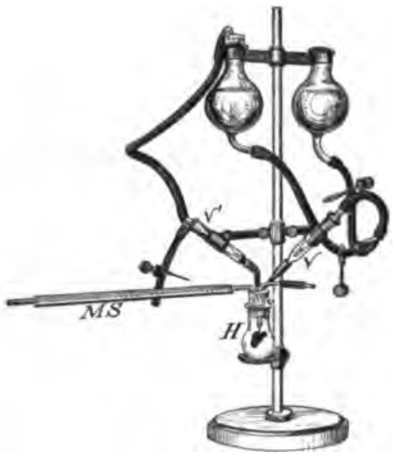

Fig. 75.—Williams' heart apparatus.

(C) The **mammalian circulation** shows similar actions although they are somewhat modified.

(a) The **isolated mammalian heart** (separated from the central nervous system) shows:

1. An increase in the strength of the muscular contractions. These are also somewhat quickened. The quickening must be attributed to the chemic irritation of the muscle from the general toxic irritant action. It will, of course, not be seen if the digitalis is injected subcutaneously or given by the mouth. The pressure during this stage will be rather increased. It is comparatively brief.

2. The quickening is followed by slowing (Fig. 76, *A*, *a*), through lengthening of the pause in diastole. This slowing is not noticed in an atropinized heart. It is probably

due to the stimulation of the vagus end-mechanism. At the same time, the beats are stronger, so that the output and pressure are increased notwithstanding the slowing.

3. After a time there is a secondary increase of rate (Fig. 76, *A*, *b*), which occurs even after atropin, and must be conceived as due to increased muscular irritability. The contractions in this stage are strong, and the output and pressure are consequently increased.

4. Following this there occurs fairly suddenly a weakening and irregularity (Fig. 76, *A*, *c*), with increasing tonus and lengthened systole and pauses. In this stage the output and the pressure will be diminished.

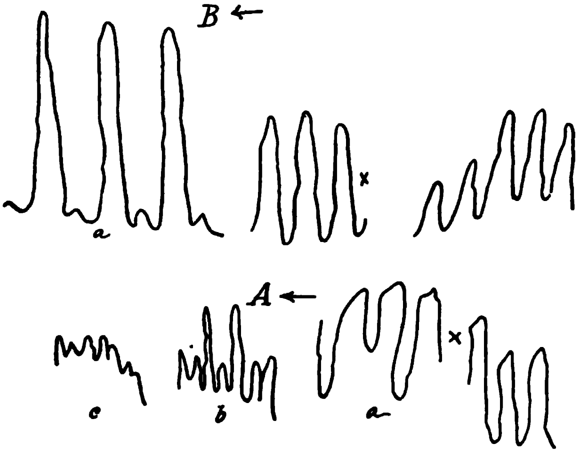

Fig. 76.—Digitalis: Cardiomyograms, dog; vagi intact. The action begins at ×. *A*: *a*, slowing; *b*, quick and strong beats; *c*, quick and weak beats. *B*: *a* shows intermittent beats.

The contractions often show rhythmic variations in strength (Fig. 76, *B*, *a*), arranging themselves into groups, or they may be entirely interrupted for a time. They give place later to diastolic or systolic standstill, according to the amount of the fatigue of the muscle. The group formation and irregularity must be attributed to the increased irritability of the cardiac muscle. Normally the ventricle contracts only in obedience to the stimuli transmitted to it from the auricle, but when the irritability of its muscle is markedly increased, it seems to become possessed of an independent rhythm, and this interferes with the contractions arising from the auricles, producing this rhythmic variation, just as beats are produced in music. When this action goes further, it results in delirium cordis. At the same time the increased muscular irritability is shown not only in independent rhythm, but also in a tendency to assume a systolic phase. But if the heart has been very much overtasked, it may not be able to assume this position, and become paralyzed in diastole.

The auricles and the right ventricle are very much less affected by the digitalis action than the ventricles. This furthers the irregularity.

Even moderate doses of digitalis lessen the *coronary circulation* in the normal heart; but this does not hold for the pathologically dilated heart, for it has been shown that an increase in the strength of weak contractions increases the flow through the coronary circulation; and a dilatation of the heart such as would occur in valvular diseases also diminishes the coronary circulation.

Summary.—To sum up the effects of digitalis on the isolated mammalian heart, one may observe:

1. Primary quickening and strengthening due to direct stimulation of the muscle.
2. Primary slowing due to stimulation of the vagus endings.
3. Secondary quickening due mainly to the increased irritability of the cardiac muscle; to a small extent, perhaps, also through paralysis of the vagus endings.
4. Secondary slowing and irregularity due to weakening and fatigue of the cardiac muscle through overstimulation.

(b) In the **intact mammal** the effect on the *vagus* is the same as in frogs. It is stimulated by digitalis both centrally and peripherally. In addition to this, there is an important contraction of the peripheral vessels from vasomotor stimulation. The combination of these three factors—the action on the cardiac muscle, on the vagus apparatus, and on the vasomotor system—reduces the action of digitalis to three main stages (Fig. 77): namely—

1. A slowed heart with increased blood pressure (*b*) (therapeutic stage).
2. Quickening of the heart with high blood pressure (*c*).
3. Quickened and irregular heart with low blood pressure (*d*).

1. The *first stage* (Fig. 77, *b*, and Fig. 78) is alone employed in therapeutics. The phenomena consist in: *Slowing of the heart, increase in the size of the individual pulse wave, and a rise in the blood pressure. The amount of blood expelled in a unit of time is increased and the velocity of the blood stream is quickened.*

The pulse is markedly slowed through a *lengthening of both systole and diastole*, but especially the former. The excursions are increased, especially the systolic (Fig. 78).

The strength of the auricles is much less affected, because they stand more thoroughly under vagus control. The synchronism of the ventricles is preserved.

The *slowing* can be accounted for by the stimulation of the vagus, this being both central and peripheral. If the vagus be divided, there will still be some slowing, but not nearly as much as when it is intact.

The vagus stimulation is *not a reflex* through the increase of blood pressure, for it is seen even in those rare cases in which digitalis lowers the pressure.

The *increased size of the individual pulse waves* is due to the more complete systole and diastole. The increase of the systole is the result of the muscular action, while the diastolic increase may be associated with the vagus stimulation.

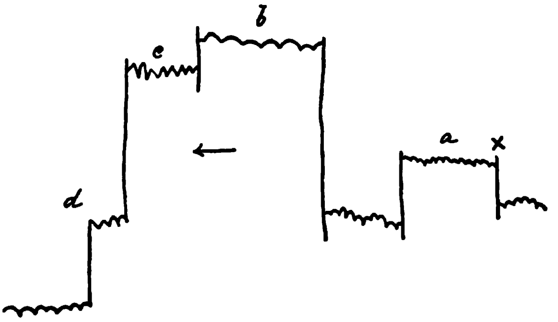

Fig. 77.—Digitalis on carotid pressure, rabbit. The action begins with a vasoconstriction at *a* (unusual in this stage); *b* shows high pressure with slow beats (first stage); *c* shows high pressure with quick beats (second stage); *d* shows low pressure with quick beats (third stage).

The *increase of blood pressure* is due to the increased volume of blood thrown out at each contraction, which occurs even when the rate is quickened. Although the slowing tends to counteract this, it is not, as a rule, sufficient to neutralize it. A beginning constriction of the arterioles also aids in this rise of blood pressure. The pressure in the pulmonary arteries will also be raised on account of the increased heart action.

There is quite a difference in the effect of digitalis on the *diastole* during the first stage, according to whether the heart is beating at its normal rate, or whether it is slow before the digitalis is administered. If the heart is beating at its normal rate, the diastole is increased by it. If, on the other hand, the heart is beating very slowly, and this slow beat is caused, not by vagus stimulation, but by weakness of the cardiac muscle, then the diastole is diminished. The explanation is that the digitalis tends to put the diastole at its full physiologic limit. In the case of the normal heart, it does so by stimulating the vagus; but in a heart which is impaired by muscular weakness, it increases the contractility and tone of the muscle, and in this way tends to lessen the diastole.

With larger doses this stage is often followed by an *exaggeration of the vagus action* (Fig. 78). The slowing is still greater than before and the heart beats become irregular, instead of the increased regularity seen in the typical first stage. The individual pulse waves become rather less in volume; the blood pressure falls. The irregularity is due in part to some muscular weakening supplementing the pure vagus stimulation.

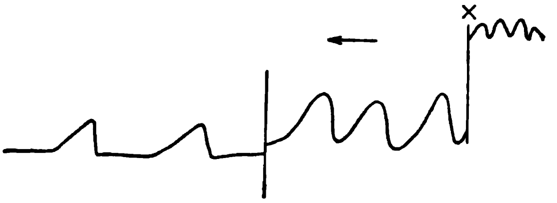

Fig. 78.—Exaggerated vagus stimulation from digitalis. Carotid pressure, dog. Action begins at ×. The beats are strong but very slow; the pressure falls.

The further stages of digitalis action are characterized by quickening of the heart, in contradistinction to the preceding stages, during which there was marked slowing.

2. The *second stage* (Fig. 77, *c*) is characterized by a *greatly accelerated rate; diminution in the size of the individual beats, and a high blood pressure. The heart is irregular and arhythmic.*

This *arhythmia* is due to the different strength of the effects upon the auricle and ventricle, as explained on page 491; and this results partly from the difference in the amount of vagus control. Many types of irregularity may result. A new injection often temporarily lessens the irregularity, through a strong stimulation of the vagus; but the final paralysis is only hastened by this. Sometimes the heart is fairly regular just before paralysis; this is when the auricle is paralyzed first and allows the ventricle to have its own rhythm.

The *increased rate* of the heart can be explained by the increased excitability of the muscle and by paralysis of the vagus apparatus, both central and peripheral. Stimulation of the vagus trunk is ineffectual (in dogs). That a greater excitability of the muscle plays a part is shown by the fact that the secondary quickening occurs even after atropin.

The *lessened pulse waves* are due to the extremely quick rate, which does not leave the heart time to expand and contract to its full extent; and, furthermore, to the onset of the systolic phase—a more permanent systolic contraction, as in the case of the frog's heart.

The *high blood pressure* is due to the extremely quick heart and to constriction of the arterioles.

3. The *third stage* (Fig. 77, *d*) shows a *very fast pulse; the heart becomes extremely irregular and passes into delirium cordis and diastolic standstill. The pulse waves are extremely small; the blood pressure falls to the abscissa.*

This *irregularity* of the third stage is due to progressive paralysis of the cardiac muscle, the vagus apparatus having already been paralyzed. The *fall of blood pressure* is due to the lessened efficiency of the irregular cardiac contractions and to the paralysis of the vasomotor apparatus which takes place at this time.

The pressure in the pulmonary arteries is little changed.

2. Rôle of the Blood-vessels.—There has been considerable discussion regarding the rôle of the blood-vessels in the rise of blood pressure by digitalis. The phenomena observed on the heart alone are quite sufficient to explain all the stages of digitalis action, and can be demonstrated with an artificial circulation apparatus (Fig. 79): first a rise of blood pressure; then quickening of the heart with blood pressure still high; then a fall of pressure with quickened heart. These are the same results as those seen in the ordinary pressure tracing. The same can be seen in the frog's heart. Here also the pressure is first raised; then in the later stages it will fall. Consequently it has been held by some eminent pharmacologists that there is no constriction of the blood-vessels. However, it is quite possible to prove that there is such a constriction in the earlier stages of digitalis action.

By injecting digitalis into a frog and *measuring the size of a* *small artery* in the foot, it can be seen that during the course of digitalis action the artery contracts to a very great extent (to about three-fourths). The *volume of the mammalian kidney*, as measured by the oncometer, diminishes. While the blood pressure rises in the arteries, the *velocity is diminished;* the arterial pressure rises, the *venous pressure falls.* Both these results can only be explained by an increase of resistance. The study of the *individual pulse waves* shows the same. If the heart is stopped, the blood pressure will come to zero; and this the quicker, the larger the arterioles. If the heart is stopped by stimulation of vagus, after the action of digitalis, the pressure falls more slowly than normal, showing that there must be increased resistance to the outflow of blood. The same is seen on the individual pulse waves. Tracings sometimes show a rise of pressure before the heart is affected (Fig. 77, *a*). Further, the *circulation time through excised organs is increased;* the action may, therefore, be peripheral, and since it takes place even in organs which have been excised for a considerable length of time,—several hours,—it must be a *muscular* action (the nervous mechanism dying much more quickly than the muscular mechanism; the excitability of unstriped muscle persists for several days under favorable conditions). The cause of the vasoconstriction is probably of the same nature as the action upon the cardiac muscle—increased tone. The existence of some peripheral action is also shown by the fact that there is some constriction after division of the cord. But some stimulation of the vasomotor center cannot be excluded.

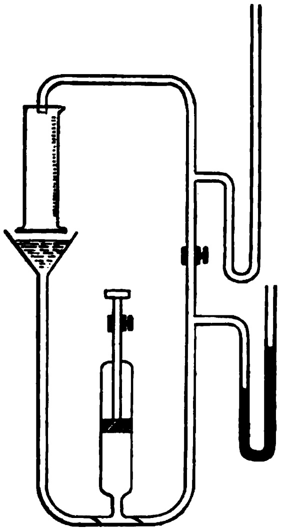

Fig. 79.—Apparatus for showing schematically the effect of the heart on blood pressure.

3. The **changes in the excretion of urine** must be regarded as secondary to the above actions. The diuretic action of digitalis in cardiac disease cannot be doubted.

Its effect in health is questioned, and seems to be to some extent variable.

It has been suggested that the increased secretion of urine after digitalis is only a manifestation of the local irritant action of the digitalis principles upon the epithelium of the kidney. This may be an accessory factor, but since the diuresis does not occur in health, it cannot be a very important one.

The action is really explained by the improvement in the circulation. If the blood pressure is low, digitalis will bring it up to the normal, or above it; and this re-establishment of the normal blood pressure, by diminishing the venous congestion and by increasing the amount of oxygenated blood carried to the kidneys, brings on the diuresis. One would expect a diuretic effect when the heart is weak, and comparatively little effect when the pressure is normal, since digitalis affects the circulation most powerfully in the former case. One might be tempted to think that the action should increase with the dose, and that there should be an increased diuresis even in normal individuals. This would be the case were it not for the constriction of the renal arterioles. The latter interferes quite seriously with its action: strophanthus, which has little vasomotor action—or the addition of nitroglycerin, which counteracts the constriction—greatly increase the diuresis.

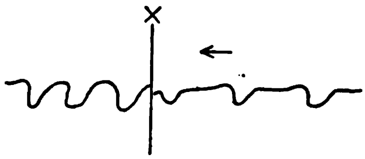

Fig. 80.—Digitalis on respiration. The action begins at ×.

The N in the urine follows the diuresis fairly closely. This is probably due to improved nutrition of the kidney cells.

4. The direct effects of digitalis upon the **central nervous system** are *purely medullary*. It stimulates the vagus center, then the vasomotor center, then the respiratory center (Fig. 80), and it may also stimulate the vomiting and convulsion centers in the medulla. It sometimes seems to have effects upon other parts of the central nervous system, but these must be considered as purely secondary to the changes in the circulation. The stimulation of the medullary centers is followed by paralysis in the same order.

The quickening of the heart occurs therefore before the fall of blood pressure.

5. Local Action of Digitalis.—This is in the nature of an irritation. Digitalis has little action on the skin, its principal effect being on the mucous membranes. If taken internally in large doses, it gives rise to *gastritis and diarrhea.* This is of some little importance, as it may interfere with the use of digitalis in certain cases. It is usually taken as a sign to stop the use of digitalis to safeguard against cumulative effects. The local irritant action is further of importance in that it interferes with the hypodermic administration of digitalis. In many cases this causes *abscess formation.*

V. DIFFERENCES IN THE MEMBERS OF THE GROUP.

The atypical members—alkalies, veratrin, and barium salts—resemble digitalis only when they are used in small doses applied directly to the frog's heart. If used in larger quantities, they paralyze the heart muscle from the start—especially the barium salts and alkalies—and produce diastolic standstill.

Copper salts, apomorphin, and acids have an action exactly opposed to that of digitalis. They lessen the force and rate, and produce diastolic standstill from direct action on the cardiac muscle.

All these drugs have more powerful effects on other parts of the system. In the case of barium salts, alkalies, and acids it would be quite impossible to get a digitalis action when administered by the stomach, because they are either not absorbed or are so changed that they cannot act as acids or alkalies.

All the regular members of the digitalis series have the typical actions which have been described, but the extent to which they act upon the three systems—vagus center, cardiac muscle, and vasomotors—differs in the different members of the group; and this is of great practical importance, because it limits their employment in several cases and makes one more useful than another. The subject has scarcely been sufficiently investigated experimentally, especially with regard to the effect upon the total circulation (as could be done by circulation time and other methods). Therapeutically it is often found that one member will do harm, whilst another will prove beneficial.

Digitoxin has the most pronounced local action, whereas this is comparatively small with digitalein; the latter might possibly be used hypodermically, but digitoxin could not be recommended.

Of the *different preparations of digitalis*, the tincture contains mainly digitoxin, digitalin, and digitophyllin; the infusion contains these to a lesser extent, and relatively more digitalein and digitonin. As it contains less of the digitoxin, it will be less irritant. The digitonin contained in it will tend to counteract the constrictor effects of the other digitalis principles, and to a less extent the action on the heart. Since diuresis is largely interfered with by the constrictor action, the infusion would be especially useful when the diuresis is an important object; whereas in those cases in which the action on the heart is the main consideration, the tincture would be more indicated.

The most important drug of the digitalis group next to digitalis is *strophanthus;* and this perhaps deserves to be the more popular. It has more of the action upon the cardiac muscle, and less of the action upon the medullary and peripheral nervous mechanism, and upon the vasomotors. This—a strong action on the cardiac muscle with a minimum action on the vessels—is exactly what is desired in most cases. It is stated that its beneficial action is not as lasting as that of digitalis, but the statement may be questioned.

Adonidin has been urged as safer than digitalis, but the evidence appears insufficient.

Erythrophlein, the alkaloid of sassy bark, has found therapeutic employment. Experience with it has not been entirely favorable. It produces a strong local irritation, and is so painful that it cannot be used hypodermically. Taken by the mouth, it causes gastritis; the medullary (vagus) and vascular effects predominate and the cardiac effect is less. The diuresis is much smaller, so that there seems to be no indication for it, and almost every contraindication.

VI. TOXICOLOGY.

The toxic effects have almost always been due to the **cumulative action.**

A person treated with digitalis may show no unpleasant symptoms for a considerable time, when, without increasing the dose, the second or third stage may set in quite suddenly and without warning. The **symptoms** of these later stages of digitalis action are those already stated: fast irregular pulse; gastro-enteritis; various nervous phenomena, which are to be referred to the disturbed circulation, and may therefore be extremely variable. The *postmortem* appearances would not be at all characteristic.

There might be some irritation of the gastro-intestinal canal.

As to the **treatment** of digitalis-poisoning, this should be mainly prophylactic—*i. e.*, directed to the avoidance of the cumulative action. This can be best done by intermitting the digitalis for several days at a time, and then giving it again for a few days, and so on. The dose should be cut down, not increased, when the pulse becomes rapid; to push the drug at this time may give temporary relief, but will hasten death.

When the poisoning has actually set in, and there is reason to suppose that digitalis is still contained in the stomach, this should be evacuated. The rest of the treatment is purely symptomatic; general stimulants should be given, because the danger in digitalis-poisoning is mainly on account of its action on the medullary centers; or, at least, very little can be done for its action on the heart. If the last stage has not yet been reached, one may counteract the constriction of the vessels by nitroglycerin.

The following gives an idea of the *relative toxicity* of some of the members of the group: To stop the frog's heart there are required of:

Digitoxin . . .	1.0	milligram	(Koppe).
Strophanthus .	0.025	"	(Gley).
Antiarin . . .	0.05 to 0.1	"	(Hedbom—R. esculenta).
	0.004	"	(Hedbom—R. temporaria).

VII. THERAPEUTIC USES.

The first stage of the digitalis action is the only one intentionally induced for therapeutic purposes. In order to appreciate its indications, it will be well to recall its phenomena. These are:

1. Slowing of the heart, with systole and diastole both lengthened.

2. Increased strength of beat, leading to greater efficiency of the individual contractions, and to an increase in the total efficiency (greater outflow per unit of time and greater pressure). This effect is most conspicuous on the left ventricle, less on the right, least on the auricle.

3. A tendency to the systolic phase.

4. A rise of blood pressure, due mainly to the increased action of the heart, but partly also to a vasoconstriction. In consequence of the latter, there is somewhat increased resistance in the circulation.

In consequence, digitalis is *indicated in all conditions of rapid pulse with low blood pressure.* It is especially useful in **valvular disease** of the heart by causing compensation, ~~preventing~~ the reflux of blood, and by relieving congestion. ~~In order~~ to understand the manner of its action in these conditions it will be well to briefly review the phenomena produced by these lesions on the simplest case, viz., **mitral insufficiency.**

The diagram (Fig. 81) will serve to illustrate these points. When an insufficiency of the mitral valve exists,—when this cannot close the auriculo-ventricular orifice,—the ventricular systole will not empty the entire contents of this chamber into the aorta; instead of the blood taking the normal path through the greater circulation, part of it will be pumped to and fro between the auricle and ventricle. What will be the result? Following the direction of the stream, there will be throughout the circulation a lessened amount of arterial blood, which implies lessened nutrition. All the organs will perform their functions less thoroughly on account of this. The heart muscle will become weaker through the lessened coronary circulation. There will be a tendency to degeneration of its muscular fibers. The kidneys will secrete less urine. The condition in the intestines will interfere with digestion and absorption. There will be an interference with the nutrition of the liver and with its functions.

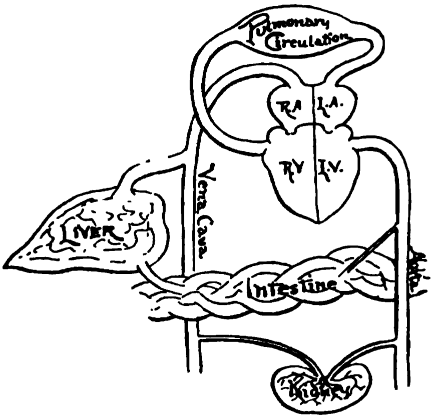

Fig. 81.—Diagram of circulation.

In the reverse direction, the regurgitation of blood from the ventricle into the auricle will interfere with the emptying of the pulmonary veins. This produces congestion of the lungs; the amount of blood flowing through the lungs will be diminished, consequently less oxygen will be carried; so that the arterial blood, which, as we noticed before, was diminished in amount, will also be diminished in oxygenating power. This congestion of the lungs tends to pulmonary effusions and edema.

The passive congestion will not stop here, but extend to the right ventricle, to the right auricle, thence to the hepatic circulation, and to all the abdominal viscera. The venous congestion interferes with the nutrition and functions of the organs. (The function of the kidney can be entirely stopped by ligating the veins coming from it, and the urine flow varies with the rapidity of the circulation through the kidneys.) This venous congestion also leads to edema and effusion, just as does ligation of the veins.

The valvular defect therefore interferes with nutrition in three ways: By the lessened amount of blood thrown into the aorta; by the lessened oxygenating power; and by the venous congestion.

The heart is, perhaps, the first organ to suffer under these conditions. Consequently it will become weaker and weaker, and in becoming weaker will render the conditions worse, establishing in this way a kind of endless chain, a *circulus viciosus*. Further, the edemas will interfere mechanically with the movements of the heart.

These are, in brief, the conditions which have to be met. This the heart itself attempts to do by hypertrophy, and as long as the hypertrophy is sufficient it is useless, and may even be harmful, to employ any drug. But let us suppose that, from any cause, the compensation has become insufficient. This may be from extra work thrown upon the heart, from an extra congestion through a cold, or from any other cause. As has been seen, even a temporary deficiency will lead to a continuous and ever-aggravating chain of symptoms, and herein lies its danger. This may be prevented by digitalis, or the chain, if already started, may be broken by it. It will be remembered that the therapeutic action of digitalis results in stronger contractions of the heart, in prolonged phases of systole and diastole, and, in consequence, in a rise of blood pressure. If the heart contracts more strongly—and we take this to be the first action of digitalis—a larger amount of blood will be thrown into the aorta and coronary circulation. The first effect will be an improved nutrition of the heart. This in itself will again cause the heart to contract more powerfully, and an endless chain of improvement will replace that of weakening. The tonic action—the fact that the digitalis tends to produce a permanent systolic condition—aids in this result in that it narrows the rings of the valves, brings them together, narrows the orifice, and in this way abolishes the effects of the distention and tends to lessen the insufficiency.

Since the heart pumps more blood, the whole arterial system will be distended and more blood will be forced through the vascular system. In the case of the kidneys, this will lead to an increased secretion of urine; in the case of the intestinal organs, to improvement in digestion and absorption, and this to improvement in the general condition of the patient.

The venous congestion will tend to be relieved. This relief—as, in the reverse case, the drag—will fall in the first place upon the lungs, and bring about better oxygenation. The lowering of the venous pressure will tend to cause absorption of the effusions, and the heart, not being interfered with, will work more efficiently. The increased secretion of urine will also aid in an elimination of the effusions. So that, just as the heart went downward by the interaction of the different causes when compensation became insufficient, it will continue the improvement through the interaction of these same causes applied in reverse direction, once it is started on this track by digitalis. Consequently the results of digitalis are more or less permanent; they last even after the remedy has been stopped. All that is necessary is to re-establish compensation, and the heart may be relied upon under ordinary conditions to maintain it. After compensation has once been re-established, the employment of digitalis is contraindicated, from the fact that it causes constriction of the blood-vessels. Relapse may, of course, occur through the same causes as primary insufficiency, and will then again require the drug.

In all cases the constriction of the peripheral vessels is an undesirable side-effect. Indeed, the indication is as much to diminish the resistance to the heart as to increase the amount of work which it is capable of doing. The constriction also interferes with the diuretic action. It is well, therefore, to counteract it as much as possible. This may be done to some extent by choosing the proper member of the group; and in this way strophanthus seems to be superior to digitalis. The same object may be accomplished in another way by the simultaneous exhibition of drugs which will produce vasodilatation, such as the nitrites. But it must be remembered that the digitalis action is lasting, whereas the nitrite action is quickly produced and lasts but a short time; so that it is better to give the two remedies separate, and not in the same prescription (digitalis perhaps five or six hours apart; the nitrites two or three hours apart).

Other forms of insufficiency: What has been said in regard to the action of digitalis on mitral insufficiency applies with equal force to insufficiency anywhere else in the circulation; for since the circulation is a closed system, it does not matter greatly where the additional force is applied or where the leak is—the result will in all cases be nearly the same. The same usefulness of digitalis will appear in most cases of **stenosis.** The increased resistance in this case leads to the same results as the leakage in the case of insufficiency, and can be combated by the same factors: viz., the strengthened beat of the heart.

The only valvular disease in which digitalis may give unfavorable results is *mitral stenosis*. It will be remembered that digitalis acts comparatively weakly upon the auricles, much more strongly on the ventricles. Consequently a mitral stenosis cannot be affected by action on the left auricle, but only through the right ventricle. This increased work of the right ventricle, combined with the stenosis of the mitral valve, will tend to produce congestion of the pulmonary vessels, consequently to lessen the oxygenation of the blood, and in this way may interfere with the nutrition of the heart. Then, again, the systolic tendency of the digitalis will render the stenosis more marked, just as it counteracted insufficiency by approaching the valvules. On the other hand, the cardiac slowing will give the lungs more time to empty into the heart. Some conditions of the action of digitalis are therefore favorable, others unfavorable; and the effect upon patients is, in consequence, variable. Some cases of mitral stenosis are benefited by digitalis, others are even made worse. The digitalis must, therefore, be carefully watched, and if it is seen that the symptoms are not improved, it should be omitted and replaced by other remedies: If the symptoms arising from low blood pressure predominate, it would be well to employ vasoconstrictors; if those from a weakened heart, vasodilators.

Another condition in which caution in the use of digitalis is recommended is *aortic insufficiency*. It is said that in this condition the prolonged diastole will give the blood in the brain a chance to gravitate back into the heart, and thus produce syncope. It is difficult to say just how much weight can be placed on this. At any rate, it would justify the caution of keeping the patient in bed so as to avoid the upright position. No harm will be done by this; on the contrary, the rest can only be beneficial.

It must be remembered that the most useful effects of digitalis are produced by a stimulation of the cardiac muscle. As a result of the better nutrition produced in this manner, the muscular fibers may afterward hypertrophy, or new fibers may possibly be formed; but the primary action of digitalis itself is confined to the already existing muscle; consequently it will be of no use if there is practically no muscle left to respond to it. It is therefore useless with a heart which has undergone marked **fatty degeneration.** And in this condition it is even contraindicated, on account of the vasoconstriction. A condition of that kind is perhaps best treated by careful exercise in such a way as to favor oxidation, to try to remove the fat in this manner. Regarding the use of digitalis in **aneurysm**: the sudden distention of the aneurysmal sac by a larger mass of blood, which would be the result of digitalis, is exactly contraindicated. The only reason why digitalis has not done more harm in this way is that it has not generally been used in large enough doses to have a marked effect.

Digitalis is sometimes employed in **fevers.** In a number of these—*e. g.*, in diphtheria—the heart is directly weakened in a manner which would be exactly counteracted by digitalis. Here, also, the vasoconstriction is contraindicated (unless there is also a vasomotor paralysis), not only on account of the increased work thrown on the heart, and which in fevers can usually not be well met by compensation because it is too acute; but also because it interferes with the loss of heat, which is so desirable in fever. Consequently, if members of the digitalis group are employed at all, they must be combined with large doses of the nitrites. In such a combination they should be very useful, and it seems as if they have hardly received sufficient trial. In certain fevers the heart is very much quickened, but without any weakening. These would not require digitalis, but rather aconite.

During the course of the administration of digitalis one frequently meets with cases of **cumulative action**; this is partly due to the very slow excretion.[1] It also requires quite a long time to produce its action; and the temptation arises to repeat the dose when the first one might have been sufficient if given time. In this way all of the first dose may not be eliminated when the second dose is taken, and a large amount of digitalis may be stored up in the system. One must also remember that less and less digitalis is required during the course of the treatment, as the heart improves. In all of these ways a cumulative action may be gradually established. Other cases develop the second or third stage of digitalis action all at once, without warning or apparent cause. These cases are probably explained by an effect on the kidney vessels, the vasomotor system suddenly becoming for some reason more sensitive, and stopping the excretion of urine and thereby of the digitalis, whilst its absorption is unimpaired.

As a prophylaxis against the cumulative action it is usually directed that the condition of the alimentary canal be watched and the digitalis stopped as soon as the irritation makes itself felt. But even without this, the administration of digitalis should be intermitted from time to time as a matter of routine. A good rule is to continue the digitalis for ten days, then intermit for four days and begin again. It is to be continued no longer than is necessary to re-establish compensation.

The **vasoconstriction** itself may be valuable in some conditions. In acute vasoconstrictor paralysis—as from shock—strychnin would be more useful, since it acts more quickly. Digitalis would only be preferred against more persistent vaso-paralysis, such as that producing one kind of dropsy.

The local actions are employed in very few members of the group: in the case of squills, as a diuretic and nauseant expectorant; and in the case of euonymus (wahoo), as a cathartic.

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[1] It takes from four to eight hours to see any marked excretion of digitalis. With most drugs the excretion is much quicker. In the case of aconite, most of the drug has left the system in three hours.

VIII. MATERIA MEDICA.

1. **Digitalis** (U.S.P.) [**Digitalis Folia**, B.P.].—*Foxglove.*—The leaves of the second year's growth of *Digitalis purpurea*, Scrophularineæ; Europe (and cultivated).

The activity of different commercial samples of Digitalis varies enormously. Of two lots under examination, one was *15 times* [!] as strong as another.

Digitalis leaves, cultivated in the United States, are fairly active.

* Other species of digitalis.

Active principles, see page 484. Fat, Mucilage, etc.

Extractum Digitalis (U.S.P.).—*Dose:* 0.015 ($\frac{1}{4}$ grain).

Extractum Digitalis Fluidum (U.S.P.).—Two-thirds alcohol; miscible with water and alcohol. *Dose:* 0.06 to 0.15 c.c. (1 to 3 minims).

⁂ *Tinctura Digitalis* (U.S.P., 15%) [12.5% B.P.].—One-half alcohol; miscible in water and alcohol. *Dose:* 0.3 to 1.5 c.c. (5 to 30 minims). This is "improved" if the leaves have been previously extracted by petroleum ether. Used mainly for cardiac action.

⁂ *Infusum Digitalis* (U.S.P., B.P.).—1.5%. *Dose:* 4 to 15 c.c. (1 to 4 drachms). This preparation must not be boiled (boiling for three hours destroys the activity almost entirely). Used mainly for diuretic action.

2. **Digitalis principles:** On account of their expense and the insolubility of the greater number in water, they have not received extensive trial. It seems, however, doubtful whether they are at all superior to the galenic preparations. The "principles" on the market are for the most part prepared from the seed. They are generally impure mixtures.

Of the many that are sometimes recommended, the following may be selected:

* *Digitoxin* (verum).—Insoluble in water. *Dose:* 0.3 to 0.6 mg. ($\frac{1}{200}$ to $\frac{1}{100}$ grain).

* *Digitalein* (verum).—Soluble in water and alcohol. *Dose:* 1 to 2 mg. ($\frac{1}{64}$ to $\frac{1}{32}$ grain).

* *Digitalin Germanicum* (mixture).—Soluble in water or alcohol. *Dose:* 1 to 2 mg. ($\frac{1}{64}$ to $\frac{1}{32}$ grain).

3. *Plants from Family of Apocynaceæ:*

Strophanthus (U.S.P.).—Seed of *S. hispidus.* Central and western Africa (used by natives as arrow-poison). Pseudo-strophanthin, etc.

Strophanthi Semina (B.P.).—Seed of S. Kombé. Strophanthin.

Other species, some entirely devoid of glucosids or action, are sometimes substituted for these.

⁂ *Tinctura S.* (U.S.P., 5%) [B.P., $2\frac{1}{2}$%].—Two-thirds alcohol; miscible with water and alcohol. *Dose:* 0.3 to 0.6 c.c. (5 to 10 minims). Seems to deserve preference over Digitalis for all purposes.

Extractum Strophanthi (B.P.).—*Dose:* 0.015 to 0.06 Gm. ($\frac{1}{4}$ to 1 grain).

Strophanthin is but little used. Most samples consist of Pseudo-strophanthin, which is nearly twice as active as the true.

Apocynum (U.S.P.).—*Canadian Hemp.*—The root of *Apocynum cannabinum.*

* Other species. North America.

Active principles, page 481. Tannin, resin.

Extractum A. Fluidum (U.S.P.).—Two-thirds alcohol, with glycerin. Miscible with water and alcohol. *Dose:* 0.3 c.c. (5 minims); as emetic, 1 to 2 c.c. (15 to 30 minims).

* Not official.
The most important preparations are marked ⁂.

* **Oleander.**—Leaves of *Nerium Oleander*, Mediterranean. Oleandrin. Since this tree is often cultivated as an ornament, it may give rise to accidental poisoning.

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4. *Family of Liliaceæ:*

Scilla (U.S.P., B.P.).—*Squills.*—The bulb of *Urginea maritima*, Mediterranean. Scillotoxin, etc.; mucilage. May be administered as * *Infusion*, 1 : 20. *Dose:* 1.5 to 5 c.c. (⅓ to 1¼ drachms).

Acetum S. (U.S.P., 10%) [B.P., 12.5%].—*Dose:* 0.6 to 3 c.c. (10 to 45 minims).

Extractum S. Fluidum (U.S.P.).—Three-fourths alcohol. *Dose:* 0.06 to 0.3 c.c. (1 to 5 minims).

⁂ *Tinctura S.* (U.S.P., 15%) [B.P., 20%].—Three-fourths alcohol. *Dose:* 0.3 to 2 c.c. (5 to 30 minims). Best preparation for diuresis.

Syrupus Scillæ (U.S.P., B.P.).—4.5% (contains acetic acid). *Dose:* 2 to 4 c.c. (½ to 1 drachm); best preparation for nauseant.

⁂ *Syrupus Scillæ Comp.* (U.S.P.).—(Hive Syrup.)—Contains Antimony (see Chap. XXVII).

Oxymel Scillæ (B.P.).—10%. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Pilula Scillæ Comp. (B.P.).—Contains Ginger and Ammoniac. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Pilula Ipecacuanhæ cum Scilla (B.P.).—(Contains 5% each of Opium and Ipecacuanha.) *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Convallaria (U.S.P.).—*Lily of the Valley.*—The root of *Convallaria majalis;* Europe, cultivated. Convallarin and Convallamarin.

Extractum C. Fluidum (U.S.P.).—One-half alcohol. *Dose:* 0.3 to 1 c.c. (5 to 15 minims).

* *Extractum C. Florum Fluidum*, N.F.

* **Polygonatum.**—Solomon's Seal.

* *Smilacina.*—False Solomon's Seal.

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5. *Family of Rannuculaceæ:*

* **Helleborus niger.**—The root; Europe. Helleborein, Helleborin.

The former is soluble in water (insoluble in alcohol) and holds forth promise for hypodermic administration. Dose: Helleborus, 0.3 to 1.3 Gm. (5 to 20 grains); Helleborein, 0.01 Gm. (1/6 grain).

* **Adonis vernalis.**—Europe.

* *Adonidin.*—Soluble in water and alcohol. *Dose:* 0.005 to 0.015 Gm. (1/12 to ¼ grain).

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6. *Other Families:*

* **Erythrophleum.**—The bark of *E. guineense*, Leguminosæ; Africa.

* *Tinctura E.*—10%. *Dose:* 0.3 to 0.6 c.c. (5 to 10 minims).

* *Erythrophlein.*—Soluble in water or alcohol. *Dose:* 0.03 to 0.06 Gm. (½ to 1 grain).

Euonymus (U.S.P.).—*Wahoo.*—Root-bark. *Euonymus atropurpureus*, Celastrineæ; North America. * Other species. *Dose:* 2 to 4 Gm. (½ to 1 drachm).

Extractum Euonymi (U.S.P.).—*Dose:* 0.1 to 0.3 Gm. (2 to 5 grains).

* *Elixir E.*, N.F.—15%. *Dose:* 15 c.c. (½ ounce).

* *Euonymin.*—*Dose:* 0.03 to 0.2 Gm. (½ to 3 grains).

Euonymus preparations are used as purgatives.

* Not official.

The most important preparations are marked ⁂.

DIURETICS

(*i. e.*, measures which increase the quantity of urine).

Although the true diuretics are, more strictly speaking, locally acting drugs and belong in Part B, the secretion of urine is so intimately connected with the circulation that the subject can perhaps be best studied in this connection.

No clear idea of the manner of action of diuretics can be formed unless one holds a definite theory on the subject of urine secretion. Whilst physiologists are by no means agreed upon the relative importance of the different factors involved in the process, we shall do well to accept a working theory, which fits in with the principal facts of pharmacology and pathology, even if it does not rest upon final and definite proof, and may need to be materially altered as more light is thrown on the subject.

Such a theory is the following:

1. The water of the urine, and the greater part of its constituents, are filtered through the endothelium of Bowman's capsule. Even here its constitution is not the same as that of serum, since certain substances, notably salts, filter much more readily than others, especially proteids. Whilst poor in proteids, this urine will have practically the same *total* salt content as the serum.

2. On account of the complicated course of the renal tubules, the urine sojourns in them for a long time, and comes into contact with a very extensive surface of deep epithelial cells. These possess an absorbing and secretory faculty, absorbing from the urine water and such substances as are of use to the organism; and secreting into it urea and uric acid. The urine will therefore become more concentrated; lose any proteids and sugar which it contains; alter the ratio of its salts; and acquire urea.[1]

The less time the urine remains in contact with this epithelium, the less will be these changes. The urine of a free diuresis is notably more rich in water, and consequently of low specific gravity. The ratio of inorganic salts to urea will be greater. The acidity, total as well as relative, will be less.

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[1] The concentration of the urine in the renal tubules may be demonstrated as follows: By injecting egg-albumen into the veins of an animal, following this in half an hour by a solution of potassium ferrocyanid, excising the kidneys and hardening thin pieces in iron-containing alcohol, the ferrocyanid is retained *in situ* by the coagulation of the albuminous urine of the tubules, and is precipitated as refractive granules by the iron. It can be seen on microscopic examination that these granules are more closely packed in the lumen of the excretory ducts than in the convoluted tubules or in Bowman's capsule, in both of which they may be discerned. No granules are seen in the bodies of any of the cells.

The **measures producing diuresis** may be grouped under three headings; they may act:

1. Through changes in the circulation;
2. By altering the composition of the blood;
3. By direct stimulation of the kidney cells.

I. EFFECT OF CIRCULATION ON URINE SECRETION.

Like all secretory processes, the rapidity of the urine secretion varies with the activity of the circulation in the gland. But the effect of the circulation on the urine is particularly large, because this is more dependent upon filtration than any of the ordinary secretory processes.[1]

Other things being equal, the rapidity of filtration will vary with the difference between the pressure of the liquids on both sides of the filtering membrane. The filtering membrane in the present case is formed by the glomerular endothelium. On one side is the pressure of the urine—practically zero; on the other, the capillary pressure, which can be varied. The filtration of urine, then, is, within certain limits, proportional to the pressure in the capillaries of the glomeruli. This pressure can be increased:

1. By **increasing the general blood pressure,** without constricting the renal vessels.

2. By dilating the renal vessels without affecting the general blood pressure.

The two are often combined in the same drug. In practice, no drug is known which will secure any of these changes in pure form.

Theoretically, (1) is obtained (*a*) by any drug whose action consists purely in raising the efficiency of the heart; (*b*) by increasing the quantity of circulating fluid.

(*a*) Of *drugs which increase the output of the heart, Digitalis* holds the first place in practice, and its group is the only one which can be used in practice.

It must be remembered, however, that the action of digitalis is not on the heart alone, but that it also constricts the peripheral vessels, and those of the kidney form no exception. Its effects are, therefore, not uniform. With moderate doses, the cardiac action will predominate in conditions in which the heart has been weakened. Hence it is always diuretic in heart disease. When the circulation is normal, the two actions go hand in hand, so that it scarcely influences the urine in healthy persons. With large doses the vasomotor effects predominate, and the quantity of urine is diminished. This vasomotor effect exists to a less degree in strophanthus or squills, and may be very largely counteracted by nitrites.

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[1] If we accept the secretory theory of urine-formation this alters nothing in the conclusions: for in that case, instead of referring diuresis directly to increased pressure, this would be conceived as acting indirectly by stimulating the renal epithelium.

(*b*) The *quantity of blood* can be increased directly by the administration of water; indirectly by the administration of salts, or other soluble substances, which withdraw it from the tissues (see salt action; Chap. XXIV, A).

Although it is well known that the arterial pressure cannot be altered for any length of time even by the intravenous injection of considerable quantities of fluid, this is by no means the case with the capillary pressure: the equality of the former is insured precisely by the rise of the latter, and the kidneys show this very prominently.

The administration of salts in such concentration as to draw water from the tissues presents such practical difficulties as to be unavailable. The administration of water, on the other hand, is one of the most useful diuretic measures for certain purposes.

Large quantities of water have a tendency to produce nausea, which can be lessened if it is given in the shape of lemonade, or of hot teas.

2. **A dilatation of the renal vessels** may be obtained by any of the usual vasodilators, the nitrites being especially efficient. However, their administration may lead to such a fall of the general blood pressure as to counteract their effects on the renal vessels. Their action on urine is consequently by no means uniform. However, they are extremely useful as additions to other diuretics, such as digitalis or caffein, which tend to constrict the renal vessels.

II. ALTERATIONS IN THE COMPOSITION OF THE BLOOD.

This subject is more thoroughly discussed in Chapter XXIV, A. It may be said now that the blood and tissues tend to pass into the urine any constituent which is abnormal, either in quality or quantity; and that, through salt action, this will carry with it an amount of water and of the normal constituent roughly proportional to the number of abnormal molecules which are removed.

Whilst any substance which is not too toxic will secure this end if injected intravenously, the substances which can be used in practice are the following:

Inorganic Acid, in dilute form: As much of a dilute solution, in the form of lemonade, as can be easily borne.

They are quite irritant to both the stomach and the kidneys, and not to be recommended, unless an acid-action is required.

Free Alkalies and Carbonates: These also render the urine alkaline. They interfere with digestion to such an extent that they are replaced by

Vegetable Acids and their Salts: These have very little action on the stomach, but are converted into carbonates in the blood, and have an alkali-action. *Potassium Acetate* is the most useful. It is given in doses of 0.3 to 2 Gm., freely diluted.

Inorganic Neutral Salts of Alkalies: Common salt may be used for the purpose. Potassium Nitrate is more effective, but possesses specific irritant qualities.

Organic Substances: The most useful are *Urea* (10 to 30 Gm.) and Saccharum Lactis (10 to 30 Gm.), both freely diluted. Most other organic substances either exert a specific irritant action, or are excreted unchanged.

Most salts also possess an irritant action, so that this group cannot be separated sharply from the following.

III. DIRECT STIMULATION OF THE KIDNEY CELLS.

The purest example of this type is *Caffein*, or more particularly Theobromin. These produce diuresis without any irritant action, whereas with most of the other "direct" diuretics, the action is more in the way of an irritation: if pushed beyond a certain point, they cause nephritis. It is not known on what part of the kidney the action of caffein is exerted. It sometimes, but not always, causes a dilatation of the arterioles, preceding the diuresis. Caffein may be given in the form of tea; or as the caffein citrate (0.2 Gm.) combined with chloral (0.5 Gm.) or Nitroglycerin (1 drop of the spirits). *Diuretin* (1 Gm.) deserves the preference. (See p. 184.)

Alterations in the composition of the blood—i.e, the introduction of any foreign substance—act largely by stimulating the renal epithelium. This stimulation is necessary in order that an increase of the quantity of blood should produce diuresis. Increase of the volume of blood by transfusion from an animal of the same species does not increase the flow of urine.

The other specific diuretics are, as has been said, **irritants.** In the doses in which they are used, they can never start a nephritis; but when such exists, they are contraindicated.

Numerous groups may be recognized:

1. Essential Oils.—See Chapter XXIX.

2. Hydrocarbons: Acohol, Urethane, Urotropin, etc. These are remarkable in that the irritant principle is not excreted by the kidneys.

3. Absorbable Metals: Especially Calomel.

4. Aromatic Series.—All the members of the series are diuretic, and this is commonly encountered as a side-action; it can be used practically in only a few instances, as with Uva Ursi (see p. 387).

5. Glucosids: These are closely related to the aromatic series. Here belong:

Broom Tops (Scoparius). These owe their diuretic action to Scoparin. The alkaloid Spartein (see p. 292) does not contribute to it. *Dose* of Scoparius (Extractum Scoparrii Fluidum): 1.0 to 4.0 c.c.

Asparagus tops seem to act similarly. They are given in 4 c.c. doses of the fluid extract.

Unless the desired object is the removal of liquid, the diuretics are best given in the form of infusions, the water materially supporting their action. And it may be said that in general a combination of diuretics acting in different ways is more efficient than any one employed alone.

Besides the quantity of urine, the individual constituents may also be influenced: thus, it may be made more acid or alkaline. Changes in the nitrogenous constituents belong under the heading of metabolism, while changes in the salts are of no great importance, as far as we know at present.

The **indications for diuretics** are as follows:

1. The *removal of liquid* from the body, in the various forms of dropsy. In this case it is well to employ them with as little fluid as possible.

If the dropsy is of *cardiac origin* drugs of the digitalis series, combined if necessary with nitroglycerin, are the most efficient diuretics, and salts may also be added. If it is of *metabolic origin*, benefits may follow salts or arsenic. If, however, it is of *renal origin*, diuretics should be avoided altogether, and recourse should be had to diaphoresis (see p. 301).

2. *To remove toxic substances from the organism*, whether these have been introduced from without or formed within the body, a free supply of water, in the form of infusions, supported by the irritants, salts, or theobromin, fulfils the indi-

cation. The hypodermic injection of large amounts of normal salt solution is a most effective method. Irritants must be avoided if the kidneys are inflamed, or if the poison is itself irritant.

3. *To dilute the urine:* This may be useful (*a*) to render it less irritant to the urinary passages in nephritis or inflammation of the bladder or urethra; it also serves a useful purpose in frequently washing out the pus and bacteria.

(*b*) To prevent the formation of calculi, or to remove concretions formed in the urinary tubules (as in oxalate-poisoning).

(*c*) To dilute irritant poisons, whose action on the kidneys is proportional to their concentration.

For the dilution of the urine, water supported by theobromin is of the greatest service.

CHAPTER XXIII.

ERGOT AND SAPOTOXIN GROUPS; SUMMARY OF TREATMENT OF COUGH.

(A) ERGOT GROUP.[1]

I. THE COMPOSITION OF ERGOT.

THE composition of ergot is still less known than that of digitalis. The statements of different investigators are quite contradictory, owing perhaps to the ready decomposition of its principles. Nor do these have any well-marked chemic properties which would aid in separating them. They are not crystallizable and do not possess any characteristic reactions; so that it may be doubted whether they have ever been isolated in pure condition.

The statements up to a few years ago were all based on the work of Kobert. Kobert claimed three active substances: (1) *ergotinic acid* (*sclerotinic acid*), which is a nitrogenous glucosid possessing an action similar to that of sapotoxin; (2) an alkaloid *cornutin*, which has a convulsive action similar to picrotoxin; (3) a resinous non-nitrogenous principle, *sphacelinic acid*.

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[1] The introduction of Ergot into Therapeutics appears of fairly recent date. The first mention of its use is found in the sixteenth century.

The most recent reliable work on this subject has been done by Jacoby. He bears out Kobert in some of his results, but goes considerably further. Jacoby accepts the ergotinic acid and the cornutin, but it would seem that this cornutin is a mixture of alkaloids. Jacoby also found another alkaloid, *secalin*, which in itself is inactive. The sphacelinic acid of Kobert is found to be a mixture. He isolated from it two elementary principles : *sphacelotoxin* and *ergochrysin*. These do not exist in the drug in a free state. The sphacelotoxin exists combined with ergochrysin as "Chrysotoxin"; with secalin, as "Secalintoxin." The following table will serve to make clear our present knowledge of the Ergot principles :

COMPOSITION OF ERGOT.

(Inactive in brackets.)

		Kobert.	Jacoby.	Jacoby.
			Primary Constituent.	Loose Compounds.
Nitrogenous Glucosids.	Concerned in Sapotoxin Action.	*Ergotinic Acid :* [1] nitrogenous glucosid. Sapotoxin action.	Accepted.	
Alkaloids.	Concerned in Convulsant Action.	*Cornutin :* [2] alkaloid of convulsant action (probably not a single substance).	Accepted. [*Secalin*, inactive.]	
N-free Resins.	Concerned in Gangrene Action.	*Sphacelinic Acid :* N-free resinous mixture with gangrene action (is a mixture of the active substances of Jacoby).	*Sphacelotoxin* : N-free resin, real active gangrene substance.	*Chrysotoxin* active. Ergochrysin + Sphacelotoxin.
			[*Ergochrysin* : N-free inactive resin.]	*Secalintoxin* active. Sphacelotoxin + Secalin.

These principles are extremely readily decomposed. The activity of ergot may be entirely lost after a few months' keeping ; one year is stated to be the length of time during which it is possible to preserve the full activity of the plant. Just what is contained in the *ordinary extracts* of ergot of the market is something which it is impossible to say; qualitatively they agree in their action with the fresh plant; quantitatively, however, there are extremely great variations, which cannot be determined by any chemic assay. The test on animals (cock's comb) is the only method which furnishes an idea of the activity of the ergot preparations. A glance at the table will show that Ergot contains *three classes* of *principles* of entirely different actions: The nitrogenous glucosid principles with *sapotoxin action;* the alkaloid having a *picrotoxin action;* and the nitrogen-free resins, sphacelotoxin and its combinations, with a *gangrene action.* It will be necessary to study each action separately before it is possible to appreciate the effects obtained from the entire drug.

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[1] Sclerotinic Acid.

[2] Ergotinin.

II. ACTION OF SPHACELOTOXIN GROUP.

The action of the sphacelotoxin group consists: (1) in a constriction of unstriped muscle, especially of the blood-vessels; (2) in a primary paralysis of the central nervous system. The cause of the *constriction of the unstriped muscle* seems to be both *central and peripheral.* It is shown most conspicuously in a *tonic spasm of the arterioles*, leading to a *rise of blood pressure*. This rise of blood pressure occurs in all animals. The spasm is extremely prolonged and quite violent; in some animals—including man, the pig, and the chicken—this constriction is so violent in some of the blood-vessels that it produces a stasis of the blood stream with coagulation and hyaline thrombosis, and, as a consequence of this, *gangrene.* This action is found only in the animals mentioned. The reason for this is probably to be sought in some difference in the anatomic structure of the blood-vessels. Possibly the capillaries are somewhat wider, or they are not under the same nervous control. There certainly must be the same kind of constriction, because the blood pressure rises in all animals. This gangrene action is perfectly typical of sphacelotoxin and is not produced to nearly the same extent by any other drug. It is seen most typically on the comb of the cock, where the arrangement of the blood-vessels appears peculiarly suitable for stasis.

An hour after the administration of the drug by the stomach, or even in shorter time if given hypodermically, the comb becomes dark and blue at the tips, and may finally slough off. Sometimes it bleaches instead of darkening.[1] The wattles are less affected. Not only the comb is affected in this manner, but in some cases also the extremities. In one recorded experiment the whole wing fell off after a few days without bleeding. These gangrene actions begin, of course, at the most distal portions, where the circulation is weakest. Similar changes occur in the comb if it is frozen; also as the result of very large hypodermic doses of Cane-sugar, Piperazin, or Chromic Acid. All these produce deep changes in the circulation. Other birds have not been investigated sufficiently. In *Hogs* the changes consist usually in pustular eruptions on the skin, especially on the tips of the ears. *Man* is very much subject to this action. The effect, of course, begins in the extremities and may lead to sloughing off of fingers or even of an entire member. This gangrene is exactly analogous to gangrene produced in any other manner. It may be wet or dry according to whether or not liquefying bacteria are present.

The same stasis is found in the vessels of the *alimentary tract*. It leads here to irritation, and in very advanced stages to ecchymosis, ulcer formation, etc. The ulcers involve particularly the lymph follicles, in which the blood supply is poorest. The stasis may lead to effusion of blood into the lumen of the intestine. The irritation combines with the direct muscular action of the ergot to produce violent *vomiting and peristalsis*. This action on the alimentary canal is also most marked in the animals mentioned, but occurs in others.

The muscular action is also shown in all animals by *contraction of the pregnant uterus*. This contraction is peristaltic in the milder stages of ergot action, and if the proper dose has been given, it will lead to the expulsion of the fetus in the normal manner without injury to either mother or fetus, and this at quite an early stage of pregnancy. In large doses it may produce a tetanic spasm, a systolic tetanus, of the uterus, which may even prevent the expulsion, and may then end in rupture of the viscus. The effect of sphacelotoxin upon the *central nervous system* consists in a

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[1] In a case of this kind examined by the author, the larger arteries possessed much thicker coats and smaller lumens than normal, so that the action of ergot probably resulted in a shutting-off of the arterial blood-supply.

depression observed in all animals. This is *usually the cause of death* in fatal doses. Convulsions are sometimes observed before death, but they are probably due to the accidental admixture of some cornutin, and not to sphacelotoxin.

III. ACTION OF CORNUTIN.

This consists mainly in a *stimulation of the medulla, followed by paralysis*, after the manner of picrotoxin.

Although the stimulation is shown most conspicuously by *clonic convulsions*, the other medullary centers—the salivary, vagus, vomiting, respiratory (Fig. 82), and vasomotor centers—are also stimulated.

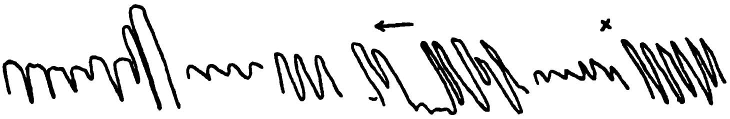

Fig. 82.—Ergot on respiration, rabbit (Lever method). Action begins at ×.

Consequently there is a *rise of blood pressure* with cornutin as well as with sphacelotoxin. A second action of cornutin is upon the *skeletal muscle* of the frog. This resembles *veratrin.* But it has no action on the heart.

IV. ERGOTINIC ACID.

The ergotinic acid has a typical sapotoxin action. Taken by the mouth it produces no effects beyond *local irritation*, as sapotoxins are not absorbed. If injected subcutaneously or intravenously, it will produce paralysis of the central nervous system and of protoplasm generally.

V. EFFECTS OF COMBINED ERGOT PRINCIPLES.

We are now in a position to study the effects of the combined ergot principles, and these can perhaps be best observed in **chronic poisoning in man.**

This chronic poisoning by ergot, "*ergotism*," was formerly very frequent endemically in consequence of the presence of ergot in flour. Ergot is a fungus which grows upon rye; and if special precautions are not taken to destroy it, it is very apt to become mixed with the grain in threshing and is ground up with the flour. In this way the population of large tracts of country have been poisoned. Since the cause has been recognized these epidemics have been less frequent, but in Russia they still play quite an important rôle.

The importance of this ergotism from our standpoint lies in the fact that it allows us to study the action of ergot. The effects of overdoses of ergot are exactly the same as those seen in chronic ergot-poisoning.

This chronic ergot-poisoning may take very *different forms*—forms which, upon superficial examination, bear almost no resemblance to one another. They were at one time classed as separate diseases. The difference is explained very readily when the different actions of the constituents of ergot are taken into account, and the fact that they may act partly on the blood-vessels and partly directly on the central nervous system. Changes which depend upon the circulation may occur almost anywhere in the body; they may appear first in one part, and later on in another, and this without definite order. The symptoms will be correspondingly variable. The initial stage is practically the same for all the different forms of ergot-poisoning. From this initial stage two principal forms diverge: the convulsive form and the gangrenous form. Toward the end the symptoms again become similar in both forms.

The **initial stage** is ushered in by *disturbance of the* **peripheral sensory apparatus.** There is *formication* in the skin and various other disturbances of cutaneous sensation. *Hyperesthesia and anesthesia* exist at the same time in different parts, or even in the same part, the skin being hyperesthetic to some forms of stimulation and anesthetic to other forms.

These disturbances of sensation *begin at the extremities and spread upward.* This distribution favors the view that they are manifestations of changes in the circulation, since these would make themselves felt first of all in the extremities. The disturbance in sensations also involves the **alimentary canal.** There is apt to be at once *voracious hunger and loss of appetite.* Digestion is much impaired on account of the disturbed circulation. Diarrhea and vomiting are very common. The vomiting is partly due to the disturbed circulation and partly to the action of the cornutin on the center. The **central sensory apparatus** also shows changes at this time. There is violent and persistent headache and central disturbances of the *special senses.* The **motor system** also begins to show abnormal symptoms, such as *twitchings* and tremors, most marked in the extremities and in the tongue.

In all these effects of ergot it is extremely difficult to say to what extent the phenomena are caused by the central, and to what extent by peripheral, actions. They are all largely dependent on disturbances in circulation, and these may in some cases be more prominent in the central nervous system; in others, peripherally.

At this point the sensory symptoms have reached their acme, and do not become any worse, but persist as they have been described. But the motor phenomena go on increasing; the twitchings pass into *spasms*, and then into permanent and often very painful *contractures*. Always beginning at the extremities, they involve the terminal phalanges of the fingers and ascend to the other joints. The facial muscles also participate. The type of these contractures shows that their origin is central. They are not absolutely persistent, but last for about half an hour; then pass off for a time, and reappear. This is very different from spasms of peripheral origin, such as those of lead-poisoning. The smooth muscles may also participate in these contractures; especially that of the bladder; so that there may be involuntary evacuation of the urine, *tenesmus*, etc.

The **pulse** is always *hard and small*, pointing to a high blood pressure. Its frequency, however, is variable. It is usually slow, due probably directly to the high pressure and to the cornutin action.

So far the symptoms, the initial stage, are common to all the different forms of ergotism; they can be accounted for partly by the change in the circulation and partly by the direct action of the ergot principles themselves. In the **second stage** the circulatory disturbances become more marked. The phenomena already seen—the disturbances of sensation and the contractures—persist; but to these are added secondary effects due to the prolonged slowing of the circulation. These may be most marked in the central nervous system or in the extremities. The former give rise to the so-called *spasmodic form* of ergotism. The predominance of stasis in the extremities produces the *gangrenous form*.

Why one action should predominate in some individuals, and another action in others, cannot be explained. Perhaps there may be some differences in the anatomic arrangement of the blood-vessels or extent of the innervation.

(A) The gangrenous form may have been indicated somewhat earlier. *Pustules* may have formed in the skin, which are due to this defect of circulation. In more marked degrees it affects the extremities. The entire member may be involved in the gangrene, which differs in no respect from any other gangrene; it has its line of demarcation, and may be *wet or dry* according to bacterial infection. The finger, toe, or limb may slough away without bleeding.

(**B**) In the **spasmodic form** the contractures pass into *tonic* and *clonic convulsions* or *epileptiform spasms.* Since any part of the central nervous system may be affected, the exact symptoms may be extremely variable. It may be repeated that they are due to a defective circulation in the central nervous system, which leads to stimulation and then to paralysis. Both forms, the gangrenous as well as the spasmodic, are therefore due to changes in circulation, and are determined by the sphacelotoxin and its compounds, the cornutin taking no part. The continued administration of cornutin does not produce in any animal symptoms resembling ergotism.

In acute ergot-poisoning—*i. e.*, where an overdose has been taken—the symptoms resemble very closely those produced by chronic ergotism, with the exception that they follow each other much more rapidly. In the acute form it is, of course, possible, and in fact likely, that the cornutin plays a part in the production of the convulsions.

The **treatment** of ergot-poisoning cannot be anything but symptomatic.

VI. THERAPEUTICS.

1. The most important property is the effect upon the **pregnant uterus**; that is to say, the setting-up of the peristaltic waves, and later on, of tetanic contraction. This has led to its use to produce *abortion.* The dose required is quite large, however; and on account of the uncertainty of ergot preparations, it is a very dangerous drug for this purpose. The action on the uterus may be too strong and it may produce rupture; or it may lead to symptoms of general poisoning.

It has been recommended in delivery at term. In this case the required dose is much smaller, and consequently it can be used much more safely. However, it seems that the temptation to give large doses is still too strong, and whenever it is used in the early stages of labor it is apt to put the uterus into tonic contraction. It is not possible to say at present whether this is due to a specific effect of ergot on the human uterus or whether too large doses are always employed. The tonic contraction of the uterus at this time may actually interfere with the delivery of the fetus; and it may also produce asphyxia of the child by too strong contraction of the uterine vessels, or pressure on the cord. If it is used at all in this stage, the dose must be small. This is very important to remember.

The principal use of ergot is to stop **postpartum hemorrhage.** It is given here at such a time that its main action will appear after the placenta is delivered. If the hemorrhage is very large and a quick action is desired, it may be injected into the gluteal muscles. It acts by contracting the vessels, and still more by producing rapid contraction of the uterine muscle, in this way obliterating the open sinuses.

It has been attempted to obtain ergot preparations which are more stable and more certain in their results than the ordinary extracts. Chrysotoxin (the combination of Ergochrysin and Sphacelotoxin) has been suggested, since it keeps for years without decomposition. But so far it has not been put upon the market, probably because the yield is quite small.

2. *The action upon other* **blood-vessels** has also been used. The *rise of blood pressure* would be indicated in cases of low blood pressure, as in shock. But ergot is not as useful as strychnin, since shock is only a temporary condition, whereas the action of ergot is lasting and sets in much too slowly.

This more prolonged rise of blood pressure has been considered of value in stopping hemorrhage in inaccessible situations.

The difficulty is that the contraction is not confined to the bleeding vessels, but extends to others, and consequently increases the general blood pressure. This may be more than enough to counterbalance the contraction at the bleeding point, and would then become harmful. But there is reason to believe that it does not act equally upon all parts of the body, so that it might still be useful in certain situations. This has not been sufficiently studied to be practically available, except for the uterus.

The reported favorable effects of ergot in *asthma* may perhaps be attributed to its counteracting a pulmonary vasodilatation.

VII. MATERIA MEDICA.

Ergota (U.S.P., B.P.) (from the French "*Ergot*," a cock's spur).—(*Secale cornutum.*)—A fungous growth from Rye. Must be of recent collection.

⁂ *Extractum Ergotæ fluidum* (U.S.P.) [*Liquidum*, B.P.].—Acidified dilute alcohol. *Dose:* 2 to 4 c.c. (½ to 1 drachm). As yet the most satisfactory preparation.

Extractum Ergotæ (U.S.P., B.P.).—Various preparations are found on the market under the names of "Ergotin," etc., but they possess no advantage over the official product. *Dose:* 0.2 to 0 6 Gm. (3 to 10 grains).

Injectio Ergotæ Hypodermica (B.P.).—30% of extract. *Dose:* 0.2 to 0.6 c.c. (3 to 10 minims).

Infusum Ergotæ (B.P.).—5%. *Dose:* 30 to 60 c.c. (1 to 2 ozs.).

Tinctura Ergotæ Ammoniata (B.P.).—25%. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Two other drugs which, in the absence of more definite knowledge, may at present be counted under the Ergot Group are Corn Smut and Cotton Root Bark.

* **Ustilago Maydis.**—Corn Smut.—A fungus analogous to Ergot, found on the corn-plant. Little is known about its composition or action, although it has been employed by the negroes for abortion, and stock-raisers have also observed that it has an ecbolic effect. Kobert states that it does not produce the ergot action on the cock's comb. He must have worked with old samples, since the author obtained the typical darkening from several different samples. However, the action is quite weak, and the drug does not deserve much attention unless it should be possible to isolate the principles in more active form.

Gossypii Radicis Cortex (U.S.P.).—The root-bark of *Gossypium herbaceum* and other species, Malvaceæ. Another ecbolic for which we are indebted to the negroes. It contains several resins. The reports of clinicians and experimenters are not favorable.

⁂ *Extractum G. R. Fluidum* (U.S.P.).—Three-fourths alcohol, one-fourth glycerin. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

VIII. ECBOLICS (OXYTOCICS) AND EMMENAGOGUES.

Ecbolics are remedies which stimulate the gravid uterus to the expulsion of the fetus. When used in the non-gravid condition, they increase the menstrual flow, and are then called *Emmenagogues*. Besides the Ergot group, one may count here:

I. All drugs which produce congestion of the abdominal organs. This always extends to the pelvic organs as well.

1. All *Drastic Purgatives*—Aloes, Myrrh, etc.

2. *Irritant Volatile Oils*, especially Savin, Thyme, Pennyroyal, and Turpentine.

3. All other *Intestinal Irritants:* Cantharides, Quinin, Digitalis, etc. A similar action is also claimed for Borax, but may be considered doubtful.

4. Application of heat or counterirritants to pelvic region or feet: hot foot- or hip-baths, mustard plasters, hot irrigations of the vagina, etc. These milder measures are only emmenagogue. When nutrition is low, they may be greatly aided by tonics.

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* Not official.

The most important preparations are marked ⁂.

It must be remembered that these irritants produce their ecbolic effect only secondarily to a gastro-enteritis. The latter may be so violent as to be fatal without accomplishing the desired result. They should not be employed for ecbolics, but at most as emmenagogues.

II. All drugs which stimulate unstriped muscle—Muscarin, Nicotin, Pilocarpin, Physostigmin, Hydrastis, etc.—may act as ecbolics, but cannot be used in practice.

IX. GENERAL HEMOSTATICS (STYPTICS);

i. e., Drugs used to arrest hemorrhage in situations not accessible to local medication.

The *local* styptics are of *no value* when given by mouth or hypodermically, but only when applied directly to the bleeding point.

The *General Measures* may be classified as follows:

1. **Mechanical:** Position, etc.

2. **Rest:** Bleeding is always increased by movement, since this breaks up the forming clots and also tends to raise the blood pressure. Extreme quiet should always be enforced, in addition to whatever other measures are taken. Morphin, Bromids, and even Alcohol may be used to secure this.

For the same reasons are contraindicated all measures which tend to produce movements, especially if these are sudden: Emetics, Purgatives, etc.

3. **Measures which change the local distribution of blood:** Cold or heat; counterirritation.

4. **Drugs lowering the general blood pressure,** either by dilating the vessels (Nitrites, Alcohol), or by depressing the heart—Aconite.

5. **Drugs producing vasoconstriction in the bleeding area:**

It will be easily appreciated that, in order to be useful in hemorrhage, a vasodilator must dilate the vessels of the general circulation, but *not* at the bleeding point. Per contra, a vasoconstrictor must constrict them at the bleeding point, but not elsewhere; in the latter case, the rise in general blood pressure might easily overcome the local constriction and make the bleeding more free.

The **selective action** of dilators and constrictors on different areas has not received the attention which the practical importance of the subject would seem to justify. The following is a summary of our present knowledge:

The *Lungs* are not much influenced by vasomotors. Hence dilatation would be indicated—*Nitrites.*

The *Brain:* The vessels leading to it are very subject to dilators, but not to constrictors. Neither measure would therefore be useful. If there is not naturally a slowing, *Aconite* would promise good results.

The *Splanchnic Area:* This is the area most sensitive to vasomotor influence, and reacts promptly to either dilators or constrictors. The latter would be indicated—*Strychnin* or *Hydrastis.*

The *Skeletal Muscles* are not readily dilated or constricted. Dilatation would be indicated—*Nitrites.*

Uterus: Strongly subject to constrictors. In Postpartum Hemorrhage: Ergot; in Menorrhea: Hydrastis and especially local treatment.

6. Specific Coagulants: *i. e.,* Drugs which increase the coagulability of the blood.

These are tried again and again for the treatment of *aneurysm* and *hemophilia.*

Whilst it is quite easy to increase the coagulability of blood outside of the body by Fibrin Ferment or $CaCl_2$; or to cause intravenous clotting by the injection of Nucleo-albumins and some other colloids—none of these measures can be expected to yield any results in therapeutics. The $CaCl_2$ is comparatively harmless, and may be given subcutaneously in 1 % to 5 % solution or by mouth, to 3 Gm. per day. It is warmly indorsed by many who have tried it.

Gelatin Injections have been introduced of recent years. Their use is purely empirical, and the reports rather contradictory, of late rather unfavorable. They are quite painful and cause some rise of temperature, often to 103° F. 100 c.c. of a sterile 1 % solution are injected slowly into the subcutaneous tissue of the thigh (*not* near the aneurysm) every ten to fifteen days. From 10 to 20 doses are said to be sufficient. It has also been used for hemorrhage in other inaccessible situations, as in the kidneys; also in *purpura hæmorrhagica.*

Ordinary styptics are generally useless in hemophilia. The inhalation of oxygen has recently been urged, on purely empirical grounds.

(B) SAPOTOXIN GROUP.

I. OCCURRENCE, ETC.

Sapotoxins are colloid principles which have a distribution in the vegetable kingdom perhaps as wide or wider than the tannins. They occur in no less than one hundred and fifty different plants, belonging to thirty different families. They contain no nitrogen and are very closely related to one another chemically; but further than this their constitution is not well understood. A great many belong to a series with the general formula $C_nH_{2n-8}O_{10}$. They decompose fairly readily, and especially under the action of alkalies, and yield bodies which have received the name of *saponins*. These differ from the sapotoxins mainly in the fact that they are physiologically inactive. However, there is no very sharp demarcation between the sapotoxins and the saponins. The two very frequently coexist in the same plant, and certain of the principles share the characters of both sapotoxins and saponins.

The sapotoxins are characterized by certain physical properties, one of which is that of *foaming* if shaken with water. This has served to give to the plants containing them such names as soap-wort, soap-bark, etc. In virtue of this property they may be used as *emulsifiers*. It will be remembered that digitonin belonged partly to this group, and on this account acted as an emulsifier, and kept the other principles of digitalis in suspension, although saponins do not dissolve insoluble substances. All the members of the group are freely soluble in water. In dilute alcohol they dissolve in proportion to the water which it contains. They are insoluble in ether and similar solvents.

The different sapotoxins differ very markedly in the *degree of their toxicity*.

The most poisonous sapotoxins are those contained in Quillaja (soap-bark) and that of Agrostemma (corn cockle). The latter differs from all the others in the fact that it may be absorbed. That contained in senega resembles the saponins very closely.

II. SUMMARY OF ACTIONS.

The action consists in a very marked *toxicity to protoplasm*, if brought in direct contact.

These principles are not absorbed from the intact mucous membrane of the alimentary canal; so that the action, if taken by the mouth, is a purely *local* one, with the one exception of the corn cockle, the principle of which seems to be capable of absorption.

III. DETAILS OF ACTION.

Locally, they exert a very marked *irritant action* on the *mucous membranes.* They have an *acrid taste* and provoke a flow of saliva (sialogogue action); if inhaled, they cause *sneezing;* if injected hypodermically, they cause *subcutaneous inflammation.* When added to defibrinated blood, they will *dissolve the corpuscles* and liberate the hemoglobin and the salts—the latter even when the corpuscles have been laked, or fixed by formaldehyd.

If they are **injected directly into the blood,** the most marked symptoms will fall upon the *central nervous system,* and are rapidly fatal. At first there are violent *convulsions;* then *paralysis,* especially of the respiratory center.

Smaller doses given by the blood cause especially *intestinal symptoms,* and death after several days by collapse. Why the symptoms are so largely intestinal is unexplained. Given subcutaneously, they produce these same symptoms, only, of course, much more slowly. If they are applied directly to skeletal or cardiac *muscle* or to nerve-trunks, these lose their irritability at once, and if the solution is fairly strong (1 %), there is rigor.

The same train of phenomena of general poisoning is obtained if these poisons are **absorbed from the stomach;** either directly, as in the case of agrostemma, or with the others after the local action has produced a corrosion of the mucous membrane. If the dose is too small for this, only the local effects are observed. These lead to symptoms of gastro-enteritis, vomiting, persistent diarrhea, etc.

IV. THERAPEUTICS.

The toxic actions on the central nervous system do not at all come into play, since there is no absorption. Only the *irritant action on the alimentary canal* needs to be considered. This bears a close resemblance to the local action of ipecac, and the therapeutic indications are the same. As *nauseants* and *emetics* they possess the advantage over ipecac that they are not at all absorbed, provided they are given in moderate doses; they therefore avoid the central action of emetin.

The property of emulsifying determines their use as *detergents* in the arts, for the cleansing of articles which are injured by alkalies.

Sarsaparilla, which owes its activity entirely to the sapotoxin or saponin which it contains, formerly enjoyed considerable reputation as an *alterative*. This is no longer accepted at the present time, and if it possesses any action at all it is simply that of a very mild nauseant.

V. MATERIA MEDICA OF SAPONIN GROUP.

Quillaja (U.S.P.) [**Quillajæ Cortex**, B.P.].—*Soap-bark.* The inner bark of *Quillaja Saponaria*, Rosaceæ; Chili and Peru. *Dose:* 1.0 to 2.0 Gm.

⁂ *Tinctura Quillajæ* (U.S.P., 20%) [B.P., 5%].—One-third alcohol. *Dose:* 2.0 to 8.0 c.c. (½ to 2 drachms).

* **Saponaria officinalis.**—*Soap-wort.*—The root or leaves of *Saponaria officinalis*, Caryophyllaceæ; temperate zone. *Dose:* 2.0 to 4.0 Gm.

Senega (U.S.P.) [**Senegæ Radix**, B.P.].—The root of *Polygala Senega*, Polygalaceæ; North America.

Extractum Senegæ Fluidum (U.S.P.).—Alkaline, three-fourths alcohol. *Dose:* 0.5 to 1.0 c c. (10 to 15 minims).

Liquor Senegæ Concentratus (B.P.).—50% alcohol. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

⁂ *Syrupus Senegæ* (U.S P.).—20%. *Dose:* 4 to 8 c.c. (1 to 2 drachms).

Infusum Senegæ (B.P.).—5%. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

⁂ *Tinctura Senegæ* (B.P.).—20%. Two-thirds alcohol. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Caulophyllum (U.S.P.).—*Blue Cohosh.*—The rhizome and roots of *Caulophyllum thalictroides*, Berberidaceæ; North America. Also contains tannin and an alkaloid and resins, about whose action very little is known. *Dose:* 0.3 to 2.0 Gm. (5 to 30 grains).

Sarsaparilla (U.S.P.).—The root of *Smilax officinalis* and some other species, Liliaceæ; tropical America.

U.S.P. Preparations.

Decoctum Sarsaparillæ Compositum: Contains Sarsaparilla, Sassafras, Guaiac, Glycyrrhiza, and Mezereum. *Dose:* 30 to 120 c.c. (1 to 4 ounces).

Extractum Sarsaparillæ Fluidum: One-third alcohol. *Dose:* 2.0 to 4.0 c.c. (½ to 1 drachm).

Extractum Sarsaparillæ Fluidum Compositum: Same ingredients as the compound decoction, with the omission of the Guaiac. *Dose:* 2 to 4 c.c.

⁂ *Syrupus Sarsaparillæ Compositus:* Contains Sarsaparilla, Glycyrrhiza, Senna, and Aromatics. *Dose:* 15 to 30 c.c. (½ to 1 ounce). Pleasant, slightly laxative vehicle.

Sarsæ Radix (B.P.).—*Jamaica Sarsaparilla.*—The root of *Smilax ornata*, Liliaceæ; Costa Rica.

Liquor Sarsæ Compositus Concentratus (B.P.).—Contains Sarsaparilla, Sassafras, Guaiac, Licorice, Mezereum. *Dose:* 8 to 30 c.c. (¼ to 1 oz.).

Extractum Sarsæ Liquidum (B.P.).—*Dose:* 4 to 15 c.c. (1 to 4 drachms).

Hemidesmi Radix (B.P.).—The root of *Hemidesmus indicus*, Asclepidaceæ.

Syrupus Hemidesmi (B.P.).—*Dose:* 2 to 4 c.c. (½ to 1 drachm).

* Not official.

The most important preparations are marked ⁂.

(C) SUMMARY OF THE TREATMENT OF COUGH.

I. PATHOLOGIC CONDITION.

The act of coughing may be defined as a coordinated reflex involving the respiratory center, and resulting in the sudden and violent expulsion of air from the lungs. It has a physiologic function in the removal of irritant substances or of accumulation of mucus from the respiratory passages. Like other reflexes, however, it tends to persist after its cause has ceased to be active; or it may become excessive. In either case it will require treatment. It must be borne in mind that cough is merely a symptom, and whilst it may be treated directly, as such; no treatment can be of permanent benefit unless it is also directed against the original cause, if this is still in operation. This cause lies most commonly in the respiratory passages, but there appear to be other conditions which may give rise to cough, or which at least may help in its production. The changes produced in the general circulation by drugs like *digitalis*, *strychnin*, or the *nitrites* are frequently beneficial. When signs of disease are present in other organs (dyspepsia, etc.), these should receive direct treatment.

II. REMEDIES AFFECTING COUGH.

Since coughing is a reflex act, it may be affected either centrally or peripherally.

(**A**) For the **central treatment** any drug may be used which depresses the respiratory center. The most useful are the members of the *Morphin Group*, and particularly *Heroin* (see p. 218). Bromids are also useful, but their action cannot be limited so nicely to the respiratory center.

(**B**) The **peripheral treatment** is to be directed against the inflammation and its attendant phenomena. It must be modified according to whether the seat of the inflammation is or is not accessible to local medication. The cause of the inflammation is usually bacterial, and requires *antiseptics*. If seated above the larynx, these may be administered by way of gargles (see p. 384). If below the larynx, inhalations of the volatile antiseptics (Creosote, etc.) are most effective. It is often attempted to secure this object by giving volatile antiseptics by the mouth, on the theory that they are excreted in sufficient concentration by the lung.

This may be considered doubtful. However, all the members of the turpentine group, when present in the blood, tend to lessen even aseptic inflammatory processes.

The *sensory irritation*, which is the immediate cause of the cough, may be diminished by demulcents or anodynes. Whilst it is only possible to apply these local measures above the larynx, yet they seem to be beneficial even in more distant irritation. It may be that the solutions spread downward over the surface of the mucous membrane.

Demulcents are colloid (gummy) substances, which appear to act simply mechanically, by excluding the air and bacteria. They play the same rôle to mucous membranes as salves do to the skin (see Chap. XXXI, A). The most important in this connection are *Acacia*, *Sugar*, *Licorice*, and the various demulcent teas.

Local anodynes act by depressing the sensory endings. They possess in this way no advantage over the central depressants, and are more difficult to apply. *Cocain* and *Atropin* may be used, the latter also in the form of the smoke from burning stramonium leaves, as for asthma. *Hydrocyanic acid* (commonly employed in the form of Syrup of Wild Cherry) also appears to act as anodyne. The most useful anodyne measure, however, consists in the inhalation of steam.

The inflammatory *congestion* may be influenced indirectly by counterirritation or compresses; or directly by local astringents, *Tannin*, *Alum*, or *Ferric Chlorid* being the most useful.

Next to the cough itself, the most conspicuous symptom of these inflammations lies in alterations in the quantity or character of the bronchial mucus. Remedies which influence these conditions are called **Expectorants.** Their employment becomes particularly important if the inflammation is seated in the bronchial divisions.

The expectorants may be divided into those which diminish the secretion of mucus, being used when this is excessive; and those which increase, and therefore liquefy, mucus, being employed in cases of "dry" cough, in which the irritation arises from thick, scanty, adherent mucus. The expectorants are also divided into *depressant*, *stimulant*, and *indifferent*, according to their effect upon the general condition of the patient. (Note that these terms do *not* refer to their effect upon the mucus!)

Expectorants which increase secretion:

Depressant: Nauseants: Ipecacuanha.
(See p. 327.) Apomorphin.
Tatar Emetic.
Sapotoxins (Senega).
Indifferent: Neutral Salts (Iodids).
Carbonates.
Pilocarpin.
Stimulant: Ammonia Salts (Carbonate or Chlorid).
Digitalis and Squills.

Expectorants which diminish secretion:

Atropin; Acids (hydrochloric); Turpentine; Aromatic Products (Benzoates, Balsams, Creosote, Tar, etc.).

When the accumulation of mucus is very great, it becomes necessary to effect its removal by the employment of emetics (see p. 327).

III. TREATMENT OF COUGH.

The underlying conditions, when known, should receive first consideration, but the symptoms may be treated at the same time. Antiseptics and demulcents are always indicated. Anodynes, central or peripheral, are only to be used when the secretion is not excessive. The choice of expectorants must be governed by the condition of the mucus, and by the general condition of the patient: the depressants are often useful if the cough is accompanied by acute fever. Their depressant action may also be abolished by combining them with strychnin, digitalis, or ammonium acetate.

It will be seen that different cases, and even the same case in its different stages, require very different treatment. The routine treatment of every case by a standard "cough-syrup" cannot be too strongly condemned. However, these compounds have a use in properly selected cases, and we therefore append a list of the most popular formulas.

IV. MATERIA MEDICA OF COMPOUND COUGH MIXTURES.

⁂ *Misturæ Glycyrrhizæ Composita* (U.S.P.).—*Brown Mixture.*—The *dose*, 4 c.c. (teaspoonful), contains: Glycyrrhiza, Sugar, Acacia; Vinum Antimonii 0.25; Tr. Opii Camphor, 0.5 c.c.; Sp. Æther. Nitr., 0.12 c.c.

⁂ *Syrupus Scillæ Compositus* (U.S.P.).—*Hive Syrup.*—*Dose:* 0.5 to 2

The most important preparations are marked ⁂.

c c. (7 to 30 minims). 1 c.c. contains Squills, Senega, and 0.002 Tartar Emetic.

⁂ *Trochisci Cubebæ* (U.S.P.).—Cubeb, Licorice, Sassafras, Tolu, Acacia. *Dose:* One every half hour.

⁂ *Elixir Picis Compositum*, N.F.: Wild Cherry, Tar, Tolu, Methyl Alcohol, *Morphin*, and Wine. The *dose*, 4 c.c. (teaspoonful), contains $\frac{1}{30}$ grain Morphin Sulphate.

⁂ *Species Pectorales*, N.F.—Althæa, Coltsfoot, Glycyrrhiza, Anise, Mullein, and Orris. Used as *infusion* 1 : 10 ad libitum.

⁂ *Syrupus Pini Strobi Compositus*, N.F.: White Pine Bark, Wild Cherry, Spikenard, Gilead, Sanguinaria, Sassafras, Morphin, Chloroform. The *dose* (4 c.c. = teaspoonful) contains 0.002 Gm. ($\frac{1}{30}$ grain) Morphin Sulphate.

PART II.—SECTION B.

DRUGS WHOSE MAIN ACTION IS A LOCAL ONE.

Introduction.—The foregoing chapters finish the class of muscle-nerve poisons—*i. e.*, of drugs whose action is specialized. These were for the most part of organic nature.

Most of the inorganic drugs, and a large number of the organic, act indifferently upon any tissue with which they come in contact. Their action may be considered as a mainly local one, even when they are introduced into the circulation and exert a widely spread action.

The line of distinction is by no means sharp, and the division must therefore always be somewhat arbitrary. We have already taken occasion to point out that the specialization of the muscle-nerve poisons is only a quantitative one—that most, if not all, also affect other structures under suitable conditions. On the other hand, most, if not all, of the local poisons show a predilection for certain tissues. None the less, the extremes are very far apart, and the greater number of poisons can easily be grouped about the one or the other, to the great convenience of systematic study.

The difference becomes at once apparent in the *underlying basis of the action.* In the case of most of the muscle-nerve poisons, the cause of the stimulation or paralysis was very obscure. Whilst many facts favor the view that they enter into some chemic combination with particular protoplasmic molecules, this theory is entirely without direct experimental proof. These chemic reactions take place only in the living molecules and are too delicate for our present methods of investigation.

On the other hand, the locally acting substances produce their effect by much coarser reactions, which we can more often oversee and comprehend, and which we can reproduce on the dead proteids in the test-tube.

Some produce violent chemic changes, such as concentrated H_2SO_4 or NaOH; others alter the water or salt content and produce precipitation in this way; still others, like the metals, form insoluble compounds; others, again, render the mineral constituents insoluble, as oxalates do calcium; others replace them by chemically similar elements, which, however, produce profound changes in the functions; this may be seen by displacing chlorids by iodids or bromids; Ca by Mg, etc.

Two great general classes of actions may be distinguished in every substance: (1) that which is specific to it—the so-called "*ion action.*" This has been so conspicuous in the muscle-nerve group that it entirely overshadowed the other, the (2) "*salt action.*" Every soluble substance obeys certain physical laws, uniform for all. In consequence of these physical properties, it exerts certain actions upon cells, which are also uniform for every substance. But in violent poisons, these are not sufficiently strong to be at all apparent. It matters very little, for instance, in what concentration a solution of strychnin is given. It does not act where it is applied, and will reach the cord in very much the same concentration, no matter what its original strength.

In other substances the ion action is very weak, and in these the salt action assumes prime importance. Since this is proportional to the concentration, and since this is the greater the less the substance is diluted by distribution through the body, and therefore greater at the point of application—the phenomena produced by them are mainly local.

Others of the local poisons—such as the heavy metals—have a marked ion action, but are not usually absorbed, so that their effects also remain confined to the point of application. They are, therefore, also proportional to the concentration.

When a substance has been absorbed it is diluted by being spread over the whole of the tissues. But it is brought together again and concentrated, when it is being excreted; so that the organs of excretion—the kidneys, skin, and mucous membranes—are the most violently affected by these local poisons—but less, of course, than the seat of their application.

Many of the ion actions belong to the domain of physiologic chemistry, and it will only be necessary to point out their application to living tissues. But the subject of salt action is as yet mainly in the hands of the pharmacologist, and must be considered more in detail. We shall confine ourselves to the present status of the subject, without entering to any great extent into its history.

CHAPTER XXIV.

GENERAL SALT ACTION; CATHARTIC SALTS.

(A) GENERAL SALT ACTION.

I. OSMOSIS.

Of the physical or salt actions, that of *osmosis* is the most important, and the most thoroughly studied.[1]

It has been discovered that when solids are brought into solution, their molecules behave precisely like those of gases, and obey the same laws. This explains all the processes of osmosis.

1. Hydrodiffusion.—If a solution of common salt be poured into a vessel, and on this some water, it will be found that, even if every conceivable precaution has been taken not to mix the liquids, the upper watery layer will after a time contain sodium chlorid molecules, and finally the composition of all layers of the liquid will be uniform.

This is explained by the fact that the salt molecules are constantly in motion, traveling freely in all directions in the liquid, in the same manner as gas molecules. A certain number will always pass toward and into the watery layer, and remain there. Other molecules will return from the upper to the lower layer. But more will go in the first direction than in the second, until the proportion of molecules in all layers of the liquid is the same. Whilst the process is infinitely more slow than in the case of gases, the final outcome is precisely the same.

2. Permeable Membranes.—Let us suppose that we separate the two liquids by a membrane, instead of placing them in direct contact. If the molecules of both salt and water pass readily through the physical pores of this membrane, the phenomena of hydrodiffusion will not be changed in any essential feature.

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[1] The student is advised to read the chapter on the molecular physics of gases and solutions in some work of physics, before studying this subject.

The process of diffusion would, of course, be somewhat slower, for a certain number of molecules would not hit upon a pore, and would rebound.

A "permeable membrane," then, slows, but does not otherwise modify, the process of hydrodiffusion.

3. **Semipermeable Membranes.**—*Osmotic Pressure.*—A "semipermeable membrane"[1] is one which allows the passage of one sort of molecules (usually the solvent), whilst impervious to another (usually the dissolved substance). The interposition of such a membrane between a solution and its solvent introduces very important modifications in the above process, and results in the development of "osmotic pressure."

Every molecule, by striking against the walls of the container, or against other molecules, exerts a certain pressure, which is precisely the same whether the substance is in the form of a gas or of a solution. If the same number of molecules per cubic space exist in two solutions separated by a permeable membrane, the pressure will be equal on each side of the membrane. The nature of the molecules is immaterial to this, as long as they all penetrate through the membrane with equal readiness.

In the case of semipermeable membranes the condition is different:

The non-diffusible molecules will all rebound from the membrane, and so remain confined to their own side. The diffusible molecules will, like gases, tend to pass through, irrespective of the other molecules, until they exist in equal concentration on each side. If a solution consisting of x molecules of salt and $(y - x)$ molecules of water per cubic centimeter were inclosed in a closed vessel and separated from water containing y molecules per cubic centimeter by a semipermeable membrane, then water would pass into the solution until it also contained y molecules of water per cubic centimeter. But it would then also contain x molecules of salt. Its total molecular concentration per cubic centimeter would therefore be $y + x$; higher by x than that of the liquid outside of the vessel. The pressure in the vessel would therefore be increased by x molecules.

This excess of pressure is called the "*Osmotic Pressure,*" or "Osmotic Tension."

Since a "gram-molecule"—the molecular equivalent of the substance expressed in grams—exerts a pressure of 22.4 atmospheres, a normal solution,[2] separated from water by a semipermeable membrane, would exert a force sufficient to drive a column of water 725 feet high! This pressure could only be reached very slowly, however, and then only if the liquid were not allowed to expand; otherwise the osmotic tension would be lessened in proportion to the dilution.

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[1] The most typical semipermeable membrane is formed of ferrocyanid of copper.

[2] A "Normal Solution" is one which contains a gram-molecule dissolved in sufficient water to make one liter.

So that if no resistance is offered to the expansion of a solution, it increases in volume, instead of increasing in pressure.

In this way a single molecule of a non-diffusible salt would theoretically be capable of attracting an infinite amount of water across a semipermeable membrane—for it is evident that the number of H_2O molecules per cubic space would always be less, by the molecules of salt, than they are in pure water.

The rapidity with which water will pass into the salt solution across the same impermeable membrane will, of course, depend upon the concentration of salt; *i. e.*, the partial vacuum of H_2O molecules in the solution. The rate of osmosis will therefore be slowed as the process progresses.

If two solutions having the same molecular concentration in dissolved substance (*i. e.*, which are "*equimolecular*") are separated by a semipermeable membrane impermeable to the dissolved substance, it is evident that no exchange of liquid will occur. Such solutions, having the same osmotic tension, are called "*isotonic*" to each other. (In physiologic literature "isotonic" usually means solutions having the same concentration as blood-serum.)

It is scarcely necessary to mention that equimolecular solutions of different substances do not contain the same percentage of the dissolved salt, but the same number of gram-molecules. The molecular weight of NaCl being 58.4; and of KCl, 74.4—a 7.44% solution of the latter would be isotonic to a 5.84% solution of the former.

If one solution has a greater molecular concentration than the other, water will pass from the weaker into the stronger solution until both have the same concentration. The stronger is then called "*hyper-isotonic*"; the weaker, "*hypo-isotonic*." Both, not being isotonic, are called "*an-isotonic*."

Another class of membranes—and by far the most important from our standpoint, since they are most generally represented in the animal body—are only **partly semipermeable**; *i. e.*, they are partly permeable to salts, though less readily than to water; and they are more permeable for some substances than for others. In this case the results will be intermediate between permeable and semipermeable membranes. They obey at first, for the main part, the laws of the latter; later, of the former. We may study this on several hypothetic examples.

1. Let us assume a membrane *perfectly permeable to water and NaCl, perfectly impermeable to proteids*, and separating solutions of these two substances. It will be plain that if the NaCl passes as readily as water, it will obey precisely the same laws as the latter; in other words, our NaCl solution will behave precisely like water, and this no matter what its concentration. With a membrane of this kind, the weakest proteid solution would be hyperisotonic to the strongest NaCl solution.

So that equimolecular solutions are isotonic only if the separating membrane is equally impermeable to both dissolved substances.

2. Let us assume a membrane which is perfectly permeable to water, and *twice as permeable to NaCl as to sugar; i. e.*, that if solutions of equal concentration of these two substances are diffused across the membrane against pure water, twice as many molecules of NaCl will pass in a given time into the latter than of sugar.[1] Let us assume that this membrane separates equimolecular solutions of these two substances. Then, in a given time, when x molecules of sugar have been passed into the NaCl solution, $2x$ molecules of NaCl will have passed into the sugar solution. A corresponding amount of water will also have passed in order to keep the concentration of the H_2O molecules constant.

So that the less easily diffusible substance possesses a higher osmotic tension than the more easily diffusible.

It will be readily understood, however, that when the ratio of NaCl molecules has become the same in both solutions, the exchange of sugar molecules will still be proceeding, and will gradually lessen the difference in osmotic tension until both solutions, in the course of time, will again become isotonic.

It is largely by virtue of this different permeability of the cell-wall to different substances that the cells of the body are able to preserve their integrity in the face of considerable changes in their environment.

All cells are relatively impermeable to proteids; their permeability to other substances is, however, very different for the individual tissues. Thus, the intestinal wall is impermeable to sulphates, which pass the kidneys with great readiness.

If a membrane is **impermeable** to both solvent and salts, no osmotic tension can, of course, be developed, since this presupposes the more ready passsage of one molecule than of another.

4. Laws of Osmosis.—For convenience, the data which have been discussed in the preceding paragraphs may be summed up in the form of laws:

1. Solutions separated by a membrane permeable to water tend to have an identical molecular composition.

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[1] The relative quickness with which different substances in equimolecular solutions pass through a given membrane is called the "*Initial Rate of Osmosis.*"

2. If the membrane is perfectly permeable to both solvent and dissolved substance, the exchange of molecules will take place without change in pressure or volume.

3. If the membrane is less permeable to the dissolved substance than to the solvent, an increase of liquid, or increase of tension, will occur in the stronger solution.

4. If a membrane is differently permeable to one dissolved substance than to another, equimolecular solutions of the less diffusible substance will be hyperisotonic to the more diffusible.

II. DISSOCIATION.

We have so far assumed that the molecular concentration of the solution is determined by the percentage of the dissolved salt divided by its molecular weight. This holds true only of certain substances, or in concentrated solutions. In dilute solutions of salts it is found that more molecules exist than would be accounted for by this formula.

The molecular concentration of solutions may be measured by a number of methods; as, for instance, by comparing their osmotic tension across semipermeable membranes. This is not very convenient. Since the boiling- and freezing-points of solutions also vary with their concentration, these, and particularly the latter, are usually chosen for these calculations.

Every mol[1] of salt per liter of solution depresses the freezing-point of water by 1.89° C., and this no matter what the substance. A solution of NaCl containing 0.584 grain NaCl per liter (equals $\frac{1}{100}$ mol) should depress the freezing-point by 0.0189°. It is found, however, that its depression is nearer to 0.03°; almost twice as great as would be expected. This difference is found only in the case of salts, not in such substances as sugar, urea, or alcohol. It can only be explained by assuming that a certain proportion of the molecules are, in this dilution, broken up into their constituent parts,—into Na and Cl,—the number being proportional to the dilution. In an infinite dilution all the molecules would be broken up, and one would have twice the theoretic depression of the freezing-point.

We can imagine that, as the molecules become separated from each other, their constituent parts also separate.

This phenomenon is called *dissociation*. Its amount is fairly constant for similar salts for the same degree of dilution. In 1 % solution of NaCl about 82.8 % of the molecules undergo this process, and about the same percentage in equimolecular solutions of KCl or NH_4Cl. Dissimilar elements, such as Mg or Ca, have a different constant.

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[1] Abbreviation for gram-molecule.

This dissociation bears a striking relation to the conductivity of salt solutions for electricity. It has been found that salt solutions conduct electricity proportionately better the more they are diluted. If, *e. g.*, a solution which contains 0.1 mol has a coefficient of conductivity which we will call "K," a solution which contains only 0.01 mol will have a coefficient higher than $\frac{K}{10}$. This increase is exactly proportional to the increased dissociation, as estimated by the freezing-point method. From this it may be concluded that electricity is conducted only by the dissociated parts. These fractions of the molecules are called **ions.**

It must not be concluded from this that the ions are identical with atoms. They have entirely different properties, and with NaCl, *e. g.*, no metallic sodium or gaseous chlorin exists in the solution. These ions are charged with positive or negative electricity, which entirely changes their character. To render this clearer, one might assume that the sodium atom enters into a new molecule-like combination with what we might call an atom of positive electricity to form the sodium ion, and the chlorin similarly with the negative. "Atom of electricity" is used here simply as a figure of speech.

If a current of electricity is passed through such a solution, the sodium ion will go to the negative pole to give up its electricity and combine there with water to form NaOH, setting free H. The chlorin ion will go to the negative pole and form HCl. The ion going to the negative pole is called kation ; that to the positive pole, anion ; since they go to the kathode and anode respectively.

IV. PHYSIOLOGIC PHENOMENA.

It may now be attempted to apply these physical processess of salt action to the phenomena of life. It is necessary to distinguish between isotonic and *an*isotonic solutions, but it will be seen that salt action always produces much the same final results, although the means by which these are brought about are exactly opposite in the different cases.

1. **Effect on Cells.**—If the molecular constitution of the medium surrounding the cells be in any way changed, this will effect, in the first place, a change in the total water or salt content of the cell. A hyperisotonic solution will

cause the withdrawal of water, and a hypoisotonic solution the withdrawal of salts. If the ratio of the different salts in the surrounding medium is not the same as that in the cells, their ratio in the latter will also be altered. Again, when salts are drawn out of the cell, it must be expected that certain of its salts will leave more quickly than others.

A salt action on the cell will, therefore, result in altering its total salt and water content and the ratio of its individual salts. These changes will react upon the proteids, just as increasing either the salt or water content of a solution will effect the precipitation of globulins in the test-tube. Other proportions will dissolve globulins. It may be assumed that similar changes occur inside the cell, with other proteid constituents as well as with the globulins.

The physiologic effects of these physical changes consist in a milder or stronger irritation, leading to quantitative or qualitative changes of function. With most cells the main changes fall upon their *metabolism*. These nutritive changes are most pronounced in the cells of lowest vitality. As a rule, pathologic formations possess less resistance than normal tissue, so that one of the most conspicuous phenomena of the general salt action is the breaking-down of pathologic formations, no matter what their origin, and whether they are chemic or anatomic.

2. If a very strong salt solution is injected directly into the circulation, the main symptoms will arise from the **central nervous system.** They consist in stimulation, with subsequent paralysis, being similar to the effects of asphyxia.

3. **Effects on the Serum.**—The primary action of the salts will be to increase the quantity of the serum, no matter in what concentration or by what channel they are introduced.

If isotonic or hypoisotonic solutions are introduced, they will pass into the blood, and so increase its quantity directly. If hyperisotonic solutions are introduced, they will draw liquid from the tissue and thus increase the volume.

The blood, however, has a very strong tendency to maintain its normal composition, much more so than the tissues. If it is attempted to alter its composition in any way, it passes the added material very rapidly into the tissues, where it is stored until it can be excreted. The composition of the *tissues* will, therefore, be changed through the salt acting on the cells, as has just been described.

The increased volume of the blood will also cause an increased flow of lymph, urine, sweat, and other liquid secretions, to effect the reduction of the ratio of serum to corpuscles to the normal. The mechanism of this passage of liquid out of the vessels into the lymph and urine has been a fruitful theme for discussion. It is most probable that several factors are involved, and to different degrees with the different secretions. Salt action, filtration, and vital secretion may all play a rôle—the last especially in the case of urine.

4. **Increase of Lymph-flow.**—Heidenhain divided the lymphogogues—the substances which produce an increased lymph-flow when injected into the circulation—into two classes.

The *first class* comprises albumoses, leech and crab-muscle extracts, etc. These act by injuring the walls of the capillaries, rendering them more permeable—resembling somewhat the action of arsenic, or of inflammation, on the vessels.

The *second class* comprises hyperisotonic solutions of soluble salts, which would therefore increase the volume of the serum by salt action. This will furnish conditions favorable to filtration—the rapidity of which is proportional to the pressure. Although it is well known that the arterial pressure is not permanently raised by the injection of even very large quantities of liquid into the blood, this does not hold of the capillary pressure. This is notably increased, and it is here that the filtration occurs. Osmosis is also concerned, for the diluted serum will be relatively richer in diffusible substances than the lymph. And, finally, there is nothing to disprove that there may not be a vital action similar to that mentioned on page 541 for the intestine. How great a part is to be ascribed to each of these factors is without our knowledge.

5. **Diuresis.**—The flow of urine is usually notably increased after the introduction of diffusible substances into the circulation—whether this be done directly or through the alimentary canal.

This urine is, of course, especially rich in the injected substance; but the absolute quantity of its other ingredients is usually also increased, for a unit of time.

This is easily understood on the doctrine of salt action, according to which the ratio of the constituents on the two sides of the membrane tends to be equal: The serum could not rid itself of, *e. g.*, NaCl without also losing some of its other salts.

A notable exception to this is that the urine is almost free from chlorids after the intravenous injection of sodium sulphate.

This last fact serves to show that vital phenomena play a much greater rôle in the formation of urine than in that of the lymph, for at a time when the urine is Cl-free, the serum has nearly its normal content of these. This agrees with the phenomenon that sugar is not excreted until it exceeds a certain percentage. These facts could not be explained on any physical basis. Nor would any physical law permit the urine to be excreted more concentrated than the serum, as is normally the case. However, osmosis does play some rôle, for the concentration of the urine, particularly of its salts, can only vary within rather narrow limits from that of the blood, and when iso-molecular solutions are injected, the total concentration of the urine is very nearly the same as that of serum.

Since urine is secreted against a practically non-proteid fluid—viz., against urine—the factor of non-diffusible constituents cannot come into play. The other factors involved in the formation of lymph may, however, be assumed to be in operation. But more stress must be laid upon the vital activity of the cells.

It is easy to see how these would be stimulated under the given conditions. An increased volume of blood will mean a quickened circulation, and this means a nutritive stimulation. But the blood is not normal, even when NaCl has been injected. The relative proportion of this salt in the serum would be altered, and this would produce a stimulation by salt action. This would be still larger in the case of salts foreign to the serum, or even with those which exist there in smaller quantity. (To make this clear, we may assume that serum contains 100 ions of Na, 100 of Cl, 10 of K, and 5 of SO_4. It is evident that the addition of 5 ions of SO_4 would cause a much greater change in the ratio of these ions than would the addition of 5 ions of Cl.)

Since the introduction of any salt will also cause an increased excretion of all other diffusible constituents of the cells, this amounts practically to a "flushing" of the body.

6. Absorption of Effusions.—When *solutions of diffusible substances* are introduced into any of the body-cavities, or under the skin, they are very rapidly absorbed, no matter what their concentration. Osmosis must necessarily play a great part in this. If the solutions are hypoisotonic, water will be absorbed until they become isotonic; hyperisotonic solutions will, of course, at first increase in volume. But even when such solutions have become equimolecular with the serum, osmosis continues to aid in their absorption; for they are still hypoisotonic to the non-diffusible solutions contained in the cells and in the circulating liquids.

The difference in the permeating power of different salts in reference to cells and the absorption of isomolecular solutions is shown very prettily by skeletal muscle.

It must be assumed that the body cells are isotonic with the serum or lymph in which they are bathed. For the frog, this would correspond to a NaCl solution of about 0.75%. If, now, the cell wall were equally permeable for all salts, one would expect that muscle laid in an equimolecular solution of any salt would neither gain nor lose water. This is not the case. If the frog's skeletal muscle is laid for eighteen hours in solutions of different salts equimolecular with the 0.75 NaCl solution, it is found to have gained or lost considerably in weight, as follows:

$NaCl$ = gain 7% of its weight.
KCl = " 40% to 50% of its weight.
$CaCl_2$ = loss 25% " " "
$LiCl$ = unchanged.

It cannot be said with certainty that these differences in absorption are due simply to the different permeability of the cell wall. The phenomenon seems to be allied to what is called *solid solution*. By this term is meant the process by which the cell takes up limited quantities of fluid into its molecular pores. Curiously enough, soap behaves exactly like muscle toward these salts.

It might at first view appear that the osmotic absorption of equimolecular salt solutions could not be applied to the *absorption of effusions*, which commonly also contain proteids. To this it may be replied that the percentage of proteids is always less in them than in the serum, and that proteids outside of the circulating body-liquids are gradually broken up into more diffusible compounds. The process, although more slow, would yet be as complete. And, as a matter of fact, the absorption of effusions or other proteid-liquids occurs much more slowly than that of salt solution.

This must not be misinterpreted as meaning that osmosis is the only process involved in the absorption of solutions and of effusions. This is probably by no means the case. It is only wished to point out that this process would be sufficient, and is presumably a potent aid. Filtration and secretion and other vital processes are no doubt concerned, but the relative rôle of their different processes is still in dispute.

7. Absorption from the Alimentary Canal.—This is probably even more dependent upon forces other than the osmosis than is absorption from serous cavities.

Filtration is very important, but vital action cannot be denied. Thus, it has been shown that in the excised and surviving intestine, immersed in a solution, a passage of fluid takes place from the lumen to the surrounding fluid, even when the two fluids are identical. This cannot on any theory be osmotic. It stops much earlier than the muscular contractions, so that it cannot be filtration, and we must be content to call it vital.

However, the time which must elapse before absorption can be complete will leave ample opportunity for osmotic processes. There will be, in the first place, a tendency to render the contents of the alimentary canal isotonic. For this, they must absorb water or salts from the tissues—first, of course, from the intestinal walls. This will result in an irritation. As this is usually mild, it will stimulate their functional activity, and lead to increased secretion, increased absorption, and increased peristalsis. The diffusible constituents of the cells—the HCl, Na_2CO_3, and possibly also the ferments—will also be drawn out by the salt action.

The presence of fluid further supplies a mechanical stimulus to the movements of the stomach and intestine. If it is notably increased, it also affects absorption. This is perhaps rather retarded in the stomach. But in the intestine it is rather increased, for the intra-intestinal pressure will be raised, and this will favor filtration, which probably constitutes a large part of the process of absorption.

Certain salts are not capable of absorption. These will tend to remain isotonic with the blood, and will therefore retain a corresponding amount of liquid; this will at once keep the intestinal contents more liquid, and—by increasing their bulk—supply a mechanical stimulus to peristalsis and produce catharsis.

We may now take up the study of these salt actions, as they can be utilized in therapeutics.

V. ACTION OF WATER AND HYPOISOTONIC SOLUTIONS.

These will increase the water content of the tissues and liquids, and will at the same time remove salts from the cells. They produce, therefore, an imbibition and a lixiviation of the tissues, and other changes resulting from this.

1. **Distilled Water.**—Lower organisms, and even fish, if placed in distilled water, lose their salts so thoroughly that they die quite quickly. This is, perhaps, not due entirely to the salt action, but to small amounts of metallic impurities (copper) from the distilling apparatus. But even when the distillation is carried on in glass, the distilled water will eventually have a fatal effect, and this before the organism has become entirely salt free. It would seem that the salt content cannot be lowered below a certain limit with impunity.

One frequently sees mention in the popular press of claimed toxic effects of drinking distilled water. These statements are entirely groundless. Distilled water is often drunk exclusively on ships, without any bad effects. It would be entirely impossible to take a sufficient amount by the stomach to remove salts from the body in such quantities as to have any deleterious influence. Even when it is injected directly into the veins of a mammal it is excreted so rapidly that it is almost impossible to introduce a sufficient quantity to be fatal.

2. The **absorption** of aqueous liquids takes place very rapidly from the intestine, while it is rather limited from the stomach. The presence of fluid rather delays the absorption of other substances from the latter organ, whereas it favors absorption in the intestine. The quantity of fluid does not, however, have any influence upon the normal utilization of food, within rather wide limits.

The popular opinion that water can be absorbed from the *skin*, is not in accord with experimental evidence. The epidermis appears to be entirely impermeable to it. Bathing in cold water will contract the cutaneous vessels, and will in this way diminish the loss of water by perspiration; while hot water will increase the loss by favoring diaphoresis.

3. The **excretion** of water takes place by the kidneys, lungs, and skin. The path which it takes in a given case will depend upon the conditions. If, for instance, the water is administered in combination with salts or urea, it will ordinarily take the same path as the latter and act as a *diuretic*. If given pure, and especially when hot (so as to favor dilatation of the cutaneous vessels), it will act as a *diaphoretic*.

4. The action of the water upon **metabolism** is important. When large quantities of liquid are taken, the nitrogen in the urine is increased, while it is diminished when the water consumption is lowered. If it is withheld for a considerable time, this increases the destruction of the body-proteids. The increased excretion of nitrogen from extensive consumption of water is undoubtedly due, in great part, to the washing out of the tissues—to the removal of ready-formed diffusible nitrogen waste products. It is therefore especially large when the body is charged with a large amount of these, as in fever; and it is then a valuable therapeutic measure for their removal. But this will lead to the breaking-up of more complicated nitrogenous molecules, so that the actual N-metabolism will be increased. This also brings with it an increase in the sulphates and phosphates in the urine.

This must be caused by the increased proteid metabolism, and not simply by the flushing of the tissues, since the chlorids are not increased in this same ratio.

The different N-metabolites are not excreted in the normal ratio.

In one experiment, for instance, in which four liters of water were administered in twenty-four hours, the urea was increased 20%, whereas the uric acid almost disappeared.

If the consumption of water is kept high for a considerable time, the nitrogen excretion does not remain at this high figure, but returns toward normal until, after three or four days, it reaches a certain level somewhat above the normal, at which it stays quite constantly.

An increased consumption of liquid may, therefore, be said to cause a considerable breaking-down of nitrogenous products, which, like all salt actions, show most strongly on pathologic formations. It has, in other words, a distinct alterative effect. This is the explanation of the action of certain weak mineral waters.

5. **Therapeutic Uses.**—These all rest upon the alteration in metabolism; the increased secretion of urine, of sweat, of nitrogen, and of waste products generally.

The indications for its use as *diuretic* and *diaphoretic* are discussed on pages 511 and 302.

The results of the **alterative action** cannot be foretold. They have been employed, especially in the treatment of *obesity*.

It is difficult to say beforehand whether the breaking-down of proteid molecules will increase or diminish the body fat. If it is only partial, it may result in the formation of fat from the proteids; if carried further, it may lead to the destruction of fat as well.

The effect of watery baths is due to an irritant action upon the epithelium and to the reflexes arising through this.

The use of water as a vehicle must be mentioned. It is very important that soluble substances be given in sufficiently dilute solutions, when it is desired to obtain their remote action to the exclusion of a local action.

VI. THE ACTION OF HYPERISOTONIC OR ISOTONIC SOLUTIONS.

This, although it exists in the case of all soluble molecules, can only be studied in substances which do not exert any marked ion actions.

1. The effects will consist principally in the withdrawal of the water, in the drying of the tissues. To this must be added the penetration of the salts into the cells, where they act as molecular foreign bodies, and where they may, in addition, cause solution or precipitation of certain of the cell constituents. Through osmotic changes they will also lead to the removal of some of the normal salts. The final

effect of these changes will be an irritation, nutritive or functional, according to the nature of the cell.

Locally, they act as mild irritants without destroying the tissues.

(a) An extensive stimulation of the **skin,** produced in this manner, and the reflexes which arise from it, explain the effects of sea and salt baths.

(b) They exert a similar stimulation upon the walls of the **alimentary canal.** This will be seen principally in the *stomach* before they suffer dilution. Their action here is a deep one, since they will stimulate all the cells with which they come into contact in the course of their absorption. Since they are quickly removed by further absorption, they do not cause any permanent change. In this way they differ from the majority of gastric irritants, which produce a superficial but persistent action. The stimulation by salts may, therefore, be continued for a considerable time, and is frequently very useful in the treatment of certain cases of "atonic" *dyspepsia.*

If salts are given in large amounts and concentrated form, the irritation may lead to a strong inflammation—to severe *gastro-enteritis,* which may be fatal in the case of some salts.

(c) The hyperisotonic salts are, of course, reduced to isotonic solutions before they are absorbed; but even then they still have considerable salt action on account of the molecular exchanges. They will, therefore, modify **metabolism** and act as **diuretics.** They may be used as adjuvants to other diuretic measures, but are especially useful in cases of dropsy dependent upon metabolic derangement.

The quantitative action of these salts will depend not only upon the absolute amount, but also upon the nature of the salt; those existing in the blood in the least amount being the most active, as has been pointed out on page 540. For this reason, the potassium salts are preferred to the sodium salts as alteratives.

The action will also be influenced by the *diffusibility* of the salt. It is evident that a salt which does not readily penetrate into the cells, but passes the kidneys without difficulty, may be excreted entirely without influencing metabolism.

2. The effects of **intravenous injection.** If hyperisotonic solutions are injected directly into the circulation, their main effects will be upon the central nervous system, lead-

ing to stimulation and then paralysis. The effects are mainly upon the medulla, leading to the same symptoms as those produced in asphyxia.

The molecular concentration of the blood may be almost double the normal in animals in which coma has been induced by excision of both kidneys. This hyperisotonic condition is therefore partly responsible for the phenomena of *uremia*.

3. Therapeutic Uses.—The effect upon the *metabolism* is uncertain in its outcome, as is the case with all alteratives.

The *diuretic* action is a very useful one. Its extent will be proportional to the amount of salt introduced. The latter is limited by the tendency to gastric irritation. The salt which has the least of this unpleasant side-action is potassium acetate.

The irritant action upon the *stomach* is useful in some cases of dyspepsia. Small doses are used for this purpose.

With larger doses a nauseant and *emetic* action appears, and may be useful.

If the salts themselves are readily absorbed, they will increase the *rapidity of absorption* from the intestinal canal. If they are not readily absorbed, they will act to some extent as *cathartics*.

Since the action of salts on blood causes the precipitation of globulins, they may be employed as *local hemostatics*. By the withdrawal of water they render the conditions unfavorable to the development of bacteria, and are, therefore, used as *preservatives for meat*, etc.

The most typical member is:

⁂ *Sodii Chloridum* (U.S.P., B.P.).—*Sodium Chlorid* (Common Salt).—$NaCl$. Soluble in 2.8 parts water, almost insoluble in alcohol.

(B) CATHARTIC SALTS.

I. MANNER OF ACTION.

The above salt actions on the body cells—and metabolism, urine, and other secretions, etc.—occur only when a soluble substance enters the blood. Certain soluble ions, however, are incapable of absorption, and these exert their salt actions in the lumen of the alimentary canal, in the manner described on page 542.

The most important preparations are marked ⁂.

If introduced in hyperisotonic condition, they will draw fluid from the body into the intestine until they are isotonic. This increase of non-absorbable liquid will tend to stimulate peristalsis mechanically. In addition, there will be a salt-stimulation from the withdrawal of liquid and salts from the cells, and some from the slight absorption of the salt itself. The total result is a catharsis—an increased quantity and number of stools of very liquid consistency.

The question has been raised, and has given rise to much discussion: Whether this fluid is drawn from the tissues? This will depend upon how much liquid there is already in the intestine. If this is not sufficient to cause the proper dilution, the tissues and blood will undoubtedly be drawn upon. The former is perhaps more often the case.

The final result is the same in both cases—catharsis and a diminution in the water content of the body, a drying of the cells and concentration of the body-liquids. The last either directly by withdrawing liquid from the tissues, or indirectly by preventing the absorption of an equivalent amount of liquid.

When a purely cathartic action is required, nearly isotonic solutions would be given; but when withdrawal of liquid is the object to be attained, more concentrated solutions would be employed.

Scarcely any of these salts are absolutely non-absorbable. The amount of absorption will be proportional to the time during which they remain in the intestine, and the osmotic exchanges to which they give rise. It will therefore be greatest from very dilute and very concentrated solutions, which must be reduced to isotony.

2. NON-ABSORBABLE IONS.

Any soluble substance must be conceived as capable of producing a salt catharsis in proportion as it is non-absorbable. But this may be modified or abolished by other factors.

Of non-absorbable ions, the *heavy metals* and *alum* produce a precipitation of proteids, and in this way an irritant or astringent effect. The earthy metals, Ca, Sr, Ba, are converted into insoluble carbonates. Oxalates and Fluorids are specifically toxic to protoplasm.

The *absorption of the more important Ions* is as follows:

(*a*) Of the *Kations*, ammonium is the most readily absorbed; then come the other alkali metals. The earthy metals are not absorbable, but magnesium is practically the only non-absorbable kation which can be utilized as a cathartic.

(*b*) Of the *Anions*, the chlorids, bromids, iodids, and acetates are rapidly absorbed. The sulphates, phosphates, tartrates, citrates, lactates, and malates are comparatively non-absorbable, and therefore possess cathartic properties.

(*c*) Of *non-dissociable compounds*, which are soluble and non-absorbable, mention may be made of certain sugars, especially mannite; as also gums and pectins.[1]

Why certain ions should be capable of absorption, others not, cannot be satisfactorily explained. Although recent investigations have shown some striking analogies between the absorption of ions by the intestine and by muscle, and the solubility of their soaps and calcium salts, it is not yet clear whether this is a mere coincidence or has a deeper meaning.

3. THERAPEUTIC USES.

The general indications for cathartics will be discussed in Chapter XXX, E.

The cathartic salts differ from vegetable and metallic cathartics in causing much less local irritation. They are therefore especially useful in general inflammatory conditions, such as fevers. They do, however, produce some irritation, and if the alimentary canal itself is the seat of inflammation, this must be reduced to a minimum. This may be done by giving them in nearly isotonic solution—such as they exist in the natural aperient mineral waters—Hunyadi or Carlsbad, etc.

They also exert an irritant action on the *stomach*, if they remain in it for a considerable time. For this reason they should be avoided with bedridden patients, for with these the passage of food from the stomach to the intestine is a rather slow one. Some exercise is always useful after taking salts, and this is one of the reasons why patients receive benefits from salt-cures in watering-places which they fail to secure at home.

Because of this slight irritation, they are preferred for the removal of liquid from the body. The addition of a small amount of a vegetable cathartic—rhubarb or senna—seems very useful. The "black draft," or compound infusion of senna, is a very good preparation.

Just as all other cathartics, they are of use in *intestinal putrefaction*, by removing the putrefying mass.

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[1] The latter have such a large molecular weight that they cannot exert any great salt action, but produce catharsis mainly mechanically by their own bulk. They form the *laxative principle of many fruits*; other fruits contain mannite or non-absorbable acid salts, tartrates, or malates.

The *choice between the salt cathartics* is very largely determined by their *taste*. The sodium sulphate has, perhaps, the most disagreeable taste; the magnesium sulphate somewhat less so. Sodium phosphate is perhaps the least disagreeable. MgO and $MgCO_3$ act as alkalies as well as cathartics.

We may now take up these salts somewhat more in detail.

4. SODIUM SULPHATE.

This is the most typical of these cathartic salts, being but very little absorbed, and absolutely free from ion action. It has no action on metabolism. On account of its very bitter taste, it is not much used, except in veterinary practice, but it forms an important ingredient of many mineral waters, *e.g.*, Carlsbad.

The kidneys are even more permeable to sodium sulphate than to NaCl, so that its intravenous injection produces a copious diuresis. The secretion of gastric juice is not increased.

The antidotal power of sulphates to carbolic acid has been pointed out on page 371. If the phenol has already been absorbed, the Na_2SO_4 must be given intravenously or hypodermically (in 2% solution).

5. SODIUM PHOSPHATE.

The phosphates also exhibit merely a local cathartic salt action. The presence of phosphorus in nerve tissue suggested the use of phosphates and phosphoric acid as nerve stimulants. There seems to be no scientific foundation for this. The phosphoric acid of the urine comes almost entirely from the phosphorus of the nucleins of the cells, not from food, and it is doubtful whether the small amount of phosphates absorbed is ever utilized.

When injected subcutaneously, they are rapidly excreted by the intestine. The feces contain phosphates even in starvation. Milk contains a large proportion of P_2O_5, and it is possible that the administration of these salts might be useful in lactation, but this has not been demonstrated. The administration of phosphates has no effect on nitrogen metabolism. Intravenously, the phosphates stimulate the vagus endings similarly to thyroiodin, and they have been claimed to be of benefit in the same conditions.

6. MAGNESIUM SALTS.

Magnesium salts are converted into the acid carbonate in the small intestine, according to the formula:

$$MgSO_4 + Na_2CO_3 + H_2O + CO_2 = Mg(HCO_3)_2 + Na_2SO_4.$$

In so far, it is quite immaterial what particular salt be given. The hydrate, carbonate, chlorid, or sulphate are all converted into this carbonate. However, in the case of the sulphate, the sodium sulphate which is formed is, of course, also cathartic, so that the effect is doubly large. The hydrate and carbonate, on the other hand, possess also the action of alkalies.

When taken by the mouth, magnesium is never absorbed in sufficient amount to have any ion action. Injected intravenously, it produces much the same effects as potassium: paralysis of the heart and the central nervous system.

These are sometimes seen in animals when the solution contained in the manometer inadvertently enters the circulation. They are usually not very lasting, since the excretion is quite rapid.

7. FERRO- AND FERRI-CYANIDS.

These belong to the typical non-absorbable salts, and are entirely free from cyanid action. They are not, however, employed as cathartics, since the HCN could conceivably be liberated from them by acids. They have, indeed, been very little studied.

Ferrocyanids form insoluble precipitates with most metals (Cu, Ni, Fe, Co, Zn) and with Strychnin, and have been suggested as chemic antidotes to these poisons.

8. MATERIA MEDICA OF CATHARTIC SALTS.

The *dose* of these is 4 to 30 Gm. (1 to 8 drachms) (teaspoonful to 2 tablespoonfuls) taken before breakfast in a tumbler of cold water.

Crude Salts.

Sodii Sulphas (U.S.P., B.P.).—*Glauber's Salt.*—$Na_2SO_4 + 10H_2O$. Soluble in 3 parts of water.

⁂ *Sodii Phosphas* (U.S.P., B.P.).—$Na_2HPO_4 + 12H_2O$. Soluble in 6 parts of water.

⁂ *Potassii et Sodii Tartras* (U.S.P.) [*Soda Tartrata*, B.P.].—*Rochelle Salt.*—$KNaC_4H_4O_6$. Soluble in 1½ parts water.

Potassi Bitartras (U.S.P.) [*Potassii Tartras Acidus*, B.P.].—*Cream of Tartar.*—$KHC_4H_4O_6$. Soluble in 200 parts water.

⁂ *Magnesii Sulphas* (U.S.P., B.P.).—*Epsom Salts.*—$MgSO_4 + 7H_2O$. Soluble in 1½ parts of water.

Magnesia (U.S.P.) [*Magnesia Levis*, B.P.].—*Calcined Magnesia.*—MgO.

⁂ *Magnesia Ponderosa* (U.S.P., B.P.).—*Heavy Magnesia.*—MgO. Prepared by rubbing light magnesia in the presence of alcohol.

Magnesii Carbonas (U.S.P.).—$(MgCO_3)_4Mg(OH)_2 + 5H_2O$.

Magnesii Carbonas Levis (B.P.).

Magnesii Carbonas Ponderosus (B.P.).

Effervescing Salts.

⁂ *Pulvis Effervescens Compositus* (U.S.P.) [*Pulvis Sodæ Tartratæ Effervescens*, B.P.].—*Seidlitz Powder.*—The blue paper contains Rochelle Salt and Sod. Bicarb.; the white, tartaric acid. Each is to be dissolved separately in a little water, the solution mixed in a large tumbler, and drunk whilst effervescing.

The most important preparations are marked ⁂.

The dose of the other effervescent salts is one to two teaspoonfuls, dissolved in cold water when needed, and drunk immediately. All the above salts are prepared in effervescent form by manufacturers. The following are official in the respective Pharmacopœias:

U.S.P.
Lithii Citras Effervescens.
Magnesii Citras Effervescens.

B.P.
Lithii Citras Effervescens.
Magnesii Sulphas Effervescens.
Sodii Citro-tartras Effervescens.
Sodii Phosphas Effervescens.
Sodii Sulphas Effervescens.

Liquid Preparations.

⁂ *Liquor Magnesii Citratis* (U.S.P.).—An effervescent preparation. *Dose*: 60 to 250 c.c. (2 to 8 ozs.).

Liquor Magnesii Carbonatis (B.P.).—A 2% carbonated solution. *Dose*. 30 to 60 c.c. (1 to 6 ozs.).

CHAPTER XXV.

ION ACTION OF SOLUBLE SALTS.

I. GENERAL CONSIDERATIONS.

THE great importance of salt actions, resting upon purely physical processes, must not be allowed to overshadow the ion action possessed by the constituent elements of these salts. The specific actions of such violently active ions as those of the cyanids or alkaloids are too conspicuous to be overlooked; but there is much more danger of this oversight in the case of substances possessing a weak action, such as sodium, potassium, calcium, etc. Indeed, these cannot for the most part be studied on intact mammals; for if injected in hyperisotonic solutions, they are obscured by the salt action; and if given in weaker solution, they are excreted too rapidly to exert any action.

The labors of numerous investigators within recent years have served to point out the importance of the ion action—even with ions which were formerly considered as indifferent, such as the Na.

1. The function into which the ion action enters most

prominently is the rhythmic contraction of the **cardiac muscle.**

A frog's heart may be kept beating for a very long time if perfused with the blood-serum of a herbivorous animal. If an isotonic solution of a non-dissociable compound—such as urea or sugar—is substituted for this, the contractions cease in a short time. The beats are not therefore sustained by a salt action. If an isotonic NaCl solution is substituted, they will continue for a longer time, but will cease quite early. One might perhaps be tempted to suppose that this deleterious action is due to the absence of colloids—and the addition of gum arabic does, indeed, prolong the contractility somewhat; but something is evidently still wanting. Numerous experiments have shown this something to be Ca and K salts, in certain proportions.[1] (Of course, the heart will also stop eventually in this case, as soon as the stock of nutritive material in its interstices is exhausted.)

One of these salts alone is not sufficient, and the heart dies very rapidly when perfused with a pure solution of any of these. Similar effects have been noticed in rhythmic contractions of skeletal muscle and in Medusæ.

Sea animals are very appropriate subjects for this study. If they are placed in pure NaCl solution of the same concentration as sea-water, they die very quickly; whereas they survive if the same quantity of NaCl is added to sea-water, nearly doubling the concentration of the latter. Here, also, the animal will live in pure NaCl if some CaCl and KCl_2 are added—one alone not being effective.

2. Theory of Ion Action.—This ion action must in all cases be conceived as chemic and not as physical.

We are at present only too much accustomed to consider the "inorganic salts" as mere admixtures of the proteid, serving a merely physical purpose. None the less, there is nothing to prove that these elements exist in the protoplasm exclusively in the form of salts as they are found in the ash. There is really every reason to assume the contrary. It is much more likely that the NaCl exists partly as sodium albuminate and as albumin chlorid. The combination of iron in hemoglobin is a familiar example of the altered state of an element in organic combination. The withdrawal of these elements, or their replacement by others, must be assumed to modify profoundly the properties of the proteid basis, and to alter the function of the cell or to kill it outright. Thus, skeletal muscle usually responds to stimulation by but a single contraction. But when placed in one-eighth normal NaCl, rhythmic contractions appear and last for several hours.

Elements which stand very near chemically have a totally dissimilar ion action. The neutralizing effects of Na and K for animals have already been mentioned. Plants, again, are able to do without any Na; but K is absolutely necessary to them, and cannot be replaced by any other alkali metal.

According to one theory, K is much more powerful in "condensing" organic molecules; thus, fusing alcohol, C_2H_5OH, with KOH will condense it to $C_6H_4(OH)_2$, whilst fusion with NaOH would acidize it. Such condensations occur in plants in the formation of fats, carbohydrates, and proteids; there is less of this in animal cells, and they do not require as much K. Sr and Mg are toxic by replacing Ca; oxalates and fluorids, by rendering it insoluble. Mg is also an essential component of extra-nuclear protoplasm. Its usefulness lies perhaps in the ease with which its compounds are dissociated, serving in this way to "transmit"—*i.e.*, temporarily take care of—acid ions.[1]

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[1] Ringer's Fluid has been found best for this purpose. It has the following composition: 100 c.c. 0.75% NaCl; 5 c.c. 0.25% $CaCl_2$; 2.5 c.c. 0.5% $NaHCO_3$; 0.75 c.c. 1% KCl. A simpler and still sufficient formula is: 100 c.c. of 0.75% NaCl solution, saturated with calcium phosphate; and 1 c.c. of a 2% KCl solution.

It is probable that all salts produce their specific action in the ion form, and not as molecules. It will be seen that metals are only toxic if dissociable into ions; and it has been shown on lower organisms that the degree of toxicity is proportional to the amount of dissociation which actually exists. (Thus, the toxicity of $CuSO_4$ to Penicillium is diminished by the addition of Na_2SO_4 to the solution—the latter diminishing the number of free Cu ions.)

II. SODIUM AND CHLORID IONS.

The least toxic of the ions are those of Na and Cl; their combinations are therefore chosen when it is desired to study the action of other ions. The latter cannot, therefore, be quite pure, but are mixed with the effects of Na or Cl. However, since the latter form such a large portion of the chemic medium of organic nature, and are always present, forming a requirement of normal functionation, this is not modified by the introduction of a slight additional quantity.

It will be found that the peripheral ion action of most of the alkalies and halogens brings them into the group of Atropin-Muscarin.

We shall now discuss the other ions in order. The free acids and alkalies show mainly the action of the H and OH ions, and will be taken up under a separate heading.

III. THE POTASSIUM ION.

The *effects* of this consist in a depression of the central nervous system and of all kinds of muscle.

The *central nervous system* is paralyzed in its whole extent. The reflexes suffer first, then the medulla. Depression of the respiratory center leads to asphyxial convulsions.

The *heart* is stimulated by small, fatigued by medium, and paralyzed by large, doses. This is seen even in the nerve-free heart of the chick's embryo, and is therefore muscular. In mammals it develops sudden slowing and irregularity, and then stops, usually before the respiration. The blood pressure remains high during the convulsions, on account of the latter (for it falls in curarized animals).

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[1] The following salt ions are absolutely necessary to plants: K, Mg, PO_4, CO_3 (Na and Cl are not necessary); Ca to all but the lower fungi and algæ. Mn forms an essential constituent of vegetable oxidizing enzymes. NO_3 and SO_4 act as nutrients.

Animals require Na, Cl, CO_3, Ca, K, Mg, I, Fe, PO_4, SO_4. It is very doubtful whether other elements existing only in traces (such as Fl) are necessary, or merely accidental.

The *skeletal muscles* become weakened and lose their irritability. A crystal of KCl applied directly to the intestine causes a local constriction ring (muscle stimulation), whereas a crystal of NaCl causes relaxation above and constriction below; *i. e.*, a true peristaltic reflex (see p. 207).

The symptoms are only seen in mammals if a potassium salt is injected directly into the circulation; they are very small if the salt is introduced hypodermically, and do not appear at all if it is taken by the stomach (except when they produce corrosion). The reason lies in the very rapid excretion. The potassium salts are largely responsible for the *toxicity of urine*, and for the phenomena of *uremia*.

The potassium ion has *not* at present *any therapeutic indication*, since the effects cannot be obtained by oral administration. The nitrate (p. 565) and bromid (p. 558) are exceptions to this. On account of its being so largely a "foreign ion" it possesses a *more pronounced alterative* salt action than Na.

The other members of the alkaline group—**lithium**, *rubidium*, *cæsium*—have practically the same action. They are of no great practical importance. Lithium is the only one of interest, and possesses an action midway between potassium and sodium. It slightly increases the N excretion. Potassium and Li urate are more soluble than the urate of Na, so that Li or K salts (acetate or nitrate) are indicated in *gout and lithiasis*.

MATERIA MEDICA.

	SOLUBILITY IN WATER.	DOSE:	
		Grams.	Grains.
Lithii Carbonas (U.S.P., B.P.).—Li_2CO_3	80	0.12 to 0.6	2 to 10
Lithii Citras (U.S.P., B.P.).—$Li_3C_6H_5O_7$	2	0.3 to 1.2	5 to 20
⁂ *Lithii Citras Effervescens* (U.S.P., B.P.)—(7%)	completely	4 to 8	1 to 2 drachms.

IV. AMMONIUM ION.

(The group NH_4.)

The ion action appears in the ammonium salts. The hydrate (ammonia) has an almost pure alkali action, and will be studied later. The ion action also appears in the *organic ammonium bases*—the amids and amins—in which the H of NH_4 has been replaced by organic radicles.

1. **Actions.**—(A) **Peripheral Nerve Endings.**—It will be remembered that the ammonium bases were discussed with the muscarin group, with which they shared the stimulation of the cardiac *vagus endings* and a *curare action* on striped muscles. These peripheral actions are much less conspicuous with the inorganic ammoniums, the stimulation of the central nervous system being much more prominent with the latter.

The most important preparations are marked ⁂.

(B) The action on the **central nervous system** consists of a *stimulation, especially of the medulla* and spinal cord. The brain is rather depressed, so that there is somnolence. The main effects are on the medulla. The *respiration* is momentarily arrested, then quickened, and finally stops in respiratory tetanus. The *circulation* usually shows a slowing of the pulse from stimulation of the vagus center; at times, however, there is a quickening, in consequence of convulsions. When it is injected intravenously, there may be a temporary quickening from chemic stimulation of the heart. Very large doses may paralyze the cardiac muscle in this way. There is always a rise of blood pressure from stimulation of the vasomotor center, involving especially the splanchnics.

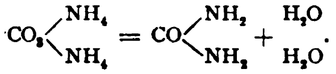
Tetanus or *convulsions* appear rather late. Their seat is mainly in the spinal cord, and they resemble strychnin spasms to a very great extent. There is, however, coma.

(C) The ammonium ion has a very marked action in increasing the **secretions,** especially saliva, mucus, and sweat. The diaphoretic action is entirely central. The action upon saliva and mucus, however, is brought about by a number of factors: (1) By a *reflex stimulation* from mucous membranes due to a salt action, which is very large in the case of ammonium salts, as they penetrate very easily; or, in the case of ammonia water and ammonium carbonate, this is brought about by the *alkaline caustic action.* (2) *Direct stimulation of the secreting centers.* (3) *Local salt action* upon the secretory cells themselves. This is especially large since the ammonia salts are *excreted largely* into the mouth *by the saliva,* as also by the lungs, mainly in the form of carbonate. In this way the local action is exerted twice, when the salt is applied and when it is excreted. (4) This excretion in the form of carbonate also tends to liquefy the mucus on account of the alkaline action.

The *methyl ammoniums* formed by the substitution of the H atoms by CH_3 have actions closely resembling the above, differing mainly in a lesser action on the cardiac muscle.

2. The **toxicology** of ammonia is really limited to ammonia water and ammonium carbonate, and these act not by their ion or salt action, but by their caustic alkaline action (Chap. XXVIII, A).

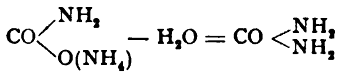
The ion action of other ammonium salts has no toxicologic importance, since they, like potassium, are absorbed too slowly and excreted too rapidly for the ion action to come into play at all. Further, the greater part of the ammonium ion is not excreted as such, but is rapidly *converted into urea*, according to the formula:



$$CO_3\begin{array}{l}\diagup NH_4\\ \diagdown NH_4\end{array} = CO\begin{array}{l}\diagup NH_2\\ \diagdown NH_2\end{array} + \begin{array}{l}H_2O\\ H_2O\end{array}.$$

Two molecules of water are split off from the ammonium carbonate and urea remains. This liberates the acid ion with which the NH_4 was combined: this will seize upon the free fixed alkali of the body, and lead to a diminished alkalinity of the serum. In this way any excess of ammonia introduced into the body is very soon eliminated, or at least ceases to act as ammonia.

But when the transformation of ammonia into urea is interfered with, an *autointoxication* may arise, with symptoms analogous to those produced by ammonium compounds. Some ammonia compound is probably a normal forerunner of urea. What this compound is, does not appear very plain, but one which has been suggested is ammonium carbaminate. The splitting-off of the H_2O from this yields urea:



$$CO\begin{array}{l}\diagup NH_2\\ \diagdown O(NH_4)\end{array} - H_2O = CO < \begin{array}{l}NH_2\\ NH_2\end{array}$$

This transformation takes place to the largest extent in the liver as the result of the action of a ferment. When this organ does not functionate properly, the dehydration may not take place, and if there is an addition of H_2O instead, ammonium carbonate results. This may give rise to at least some of the symptoms which are noticed in cases of disease of the liver. The symptoms of uremia also resemble those of ammonium-poisoning. However, the ammonia is not increased in the blood, in either uremia or in acute yellow atrophy of the liver. A notable increase occurs in diabetic coma.

3. **Therapeutic Uses.**—The properties which have a therapeutic importance are the stimulating effect upon the central nervous system and the local action upon secretion. The stimulating effect upon the *central nervous system* may conceivably be a direct one, but, as has been pointed out, this must be very slight, for the ion does not remain in the body a sufficient length of time to exert any marked action. To attempt to modify the effect of an acid by giving it as an ammonium salt is scarcely scientific; for besides the quick excretion, the amount which could be given in this way it too small to have any influence.

Ammonia water and the carbonate have, however, a very marked stimulating effect upon the central nervous system, but this is *reflex* and is dependent only upon the local caustic action, enhanced by their volatility. This reflex stimulation —which is shown mainly on the medulla—can be produced by other means, but the inhalation of ammonia is one of the most efficient. The aromatic spirits of ammonia—15 to 30 drops to the tumbler of water—is one of the best ways of producing these effects. In the form of smelling salts it is frequently used in fainting and in shock.

The stimulation of the *respiratory center* is useful in cough, asthma, edema of the lungs, pneumonia, or any case where the respiration is interfered with. The stimulation of the *sweat center* is useful as a diaphoretic measure, in colds, fever, etc. (see p. 304). For this purpose the Liquor Ammoniæ Acetatis is employed; this is probably absorbed somewhat more readily than other ammonium salts, so that there is perhaps some direct stimulation of the central nervous system.

The *local "expectorant" action* and the increased secretion of mucus have already been discussed and the manner in which this is produced pointed out; that is to say, by reflex irritation, possibly some direct stimulation of the central nervous system, by the salt action, and the excretion of ammonia in the form of ammonium carbonate. These probably suffice to explain the almost specific action upon the secretion of mucus. This is increased in amount and rendered thinner and less tenacious. When it is desired to affect the secretions low down in the trachea and bronchioles, the ammonia salt is very frequently administered in the form of inhalation of ammonium chlorid, produced in a finely divided state by bringing together the vapors of ammonia and hydrochloric acid. This can be inhaled to the finer divisions of the bronchi.

The somewhat stronger salt action of concentrated solutions of ammonium salts, leading to gastric irritation and vomiting, has been discussed with the emetics (see p. 326).

Ammonium chlorid has also been recommended as a specific in tropical dysentery. The number of observations upon its use is hardly sufficient to make a final decision as to its value. This could only be explained by a specific toxic action on the amœba coli.

4. Materia Medica.—

⁂ *Ammonii Carbonas* (U.S.P., B.P.).—(*Hartshorn, Baker's Ammonia, Sal Volatile*).—$NH_4HCO_3.NH_4.NH_2CO_2$. Soluble in 5 parts water. *Dose:* 0.12 to 1.0 Gm. (2 to 15 grains), largely diluted.

The most important drugs are marked ⁂.

⁂ *Spiritus Ammoniæ Aromaticus* (U.S.P., B.P.).—(*Aromatic Ammonia*):

Ammon. Carb.	3.4	*Dose:* 2 to 8 c.c. (½ to 2 drachms). Diluted with a glass of water.
Ammonia Water . . .	9.0	
Aromatic Oils		
Alcohol	70.0	
Water to	100.0	

⁂ *Ammonii Chloridum* (U.S.P., B.P.).—(*Sal Ammoniac.*)—Soluble in 3 parts water, almost insol. in alcohol. *Dose:* 0.06 to 2 Gm. (1 to 30 grains). Best given in the form of:

⁂ *Trochisci Ammonii Chloridi* (U.S.P.).—Each 0.12 Gm. (2 grains).

⁂ *Liquor Ammonii Acetatis* (U.S.P., B.P.).—(*Spiritus Mindereri*).—Made when required by neutralizing Ammonium Carbonate with Acetic Acid. *Dose:* 2 to 30 c.c. (½ to 8 drachms) (diaphoretic).

V. THE BROMID ION.

1. The **action** of this is precisely the opposite of that of ammonium. It consists in a depression of the central nervous system, similar to that produced by potassium.

The *experimental data* in regard to this action are as yet very unsatisfactory. The doses which can be introduced do not produce any decisive phenomena in animals. The most conspicuous effects are observed in epilepsy. But here the KBr is far more efficient than NaBr; and since other K salts also exert a similar action, some authors have regarded the Br ion as entirely inactive. This does not do justice to the evidence—for these other K salts are much less efficient than the bromid, and NaBr is also effective. The K aids, however, and KBr are always preferred.

In any case the action of the Br ion is small, and consists in a depression, rather than in abolition, of function. The action is studied in much the best manner in man, because slight changes in the central nervous system are extremely difficult to observe in animals. In man it leads to depression of mental activity in general, but certain kinds are much more readily influenced than others. These differences have not been sufficiently studied. The defect seems to be in appreciation rather than in perception; just as in the case of morphin, it seems that the stimuli reach the brain, but are not appreciated in the ordinary manner. But the power of observation is not interfered with in moderate doses. In the case of reflexes it seems to be the *connecting link* between the central cells which suffers, so that the main effect is not upon the primary reflex, but upon other reflexes which may arise from this. So also a stimulation of the motor areas which, under the conditions of the experiment, gives rise to general epileptiform convul-

The most important preparations are marked ⁂.

sions, will, after the administration of a bromid, be confined to the area directly stimulated. If a bromid is administered to animals under strychnin, the effect of stimulation does not have much tendency to spread, whilst the primary reflex, say the patellar, will still be exaggerated. Although the main interference is with the spreading of the impulse to other parts, the direct *reflexes* are also diminished. This was utilized before the days of local anesthetics, for instance, in the examination of the throat.

Large doses of potassium bromid may have an action upon the heart, depending entirely upon the potassium ion.

2. If the administration of bromids is continued for a considerable length of time, there results a series of symptoms grouped under the name "**bromism.**" These depend on a local irritant action, which finds expression in gastritis, in acne, in coryza, etc. It is due partly to the salt action of the bromin salt, also probably in part to a decomposition of the bromid, with liberation of bromic acid and bromin, by the free acids existing in these situations: in the stomach, hydrochloric acid; in the mouth, large quantities of carbonic acid; in the skin, especially the acid secretions of the sebaceous glands. It is favored by insufficiency of the kidney. It is more easily produced in old age.

3. The **excretion** of the bromid begins very quickly, but lasts for a very long time, traces appearing in the urine for over sixty-five days. The main amount is found in the blood, and next to this in the brain and kidneys; the liver, bile, and spleen are free from it. This slow excretion lends support to the theory that the bromin enters into combinations in the body, and it is very likely that it may to some extent take the place of the chlorin in its protoplasmic combinations. The excretion of chlorid is increased. The administration of NaCl quickens the excretion of the Br, and lessens the symptoms of bromism.

Very likely the ion action depends upon this substitution of bromin for chlorin. The P_2O_5 of the urine is somewhat diminished, the N increased, but the metabolic action is not large.

The bromin action can only be obtained from fairly large doses, is always rather small, and is not usually seen until the administration has been continued for some time.

No effect can be expected from the bromin in salts which are used in small doses—*e. g.*, bromid of quinin, of arsenic, etc. In these it can only be useful by influencing the solubility or dissociability of the compound.

The **effects of the continued administration** of bromids consist in an exaggeration of the effects observed after a single dose. There is dullness, bad memory, sometimes aphasia; and, in general, lowered activity of the central nervous system. Partly on account of this, partly on account of the gastritis and general irritant action, there is a lowered resistance on the part of the patient. All these symptoms seem to disappear quite quickly on the withdrawal of the drug, persisting only a little longer than the bromin remains in the body.

4. **Therapeutics.**—Bromids are used mainly against epilepsy. They were introduced for this purpose in 1853. They do not seem to be efficient in all cases, probably because epilepsy has different causes. The successful cases amount to something like 90% in idiopathic epilepsy.[1] Large doses must be employed and continued for some time. The potassium bromid is the more efficient salt. On the other hand, the calcium or strontium bromids are less irritant to the stomach, since they must be decomposed before being absorbed, and the bromid ion is therefore liberated more slowly. The attacks of epilepsy usually return as soon as the remedy is removed. In some few cases, however, a permanent effect seems to have been obtained. It is possible that this cure was not due to the bromin, but was spontaneous.[2]

It has also been attempted to employ bromin against other diseases which rest upon a heightened irritability of the central nervous system—for instance *chorea and tetanus.* The results have been variable; sometimes it has been efficient, and at other times not. It is useful, however, in all cases of *overaction of the brain*—worry, etc.—and all the conditions which arise from these—say, insomnia and nervousness. It is of no value in pain. The depression which it produces is rather lasting, so that it is not indicated as an ordinary hypnotic. It is useful in all cases where we have an *exaggeration of reflexes*, such, for instance, as some cases of cough; in *incontinence of urine* if this results from overaction of the detrusor center. It may be useful in *reflex vomiting*. It has been recommended in both sea-sickness and pregnancy; the results have been variable. It is useful in *pertussis* (1 Gm. per day for a child one year old). Large doses are often curative in acute mania—as much as 100 Gm. may be given, distributed over three days.

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[1] Binz gives the following compilation:
Permanent cures, 40%.
Total abolition as long as drug is continued, 12%.
Diminished in number and violence of attacks, 83%.
No influence, 2½%.
Number of attacks increased, 2½%.

[2] The treatment of Epilepsy: Besides the bromids, the following drugs have been used empirically: Opium, Valerian, Belladonna, Zinc Oxid, Chloral, Adonis Vernalis. The results are not very brilliant, and their trial can only be recommended when bromids have failed or are for any reason badly borne. No treatment will be successful except it be joined with a careful regulation of diet and general hygiene, excesses of all kinds being strictly proscribed.

The inhalation of Amyl Nitrite is sometimes useful during the attack.

As to the manner of administration, the bromids should always be largely diluted, and are best flavored with peppermint or wintergreen.

5. Materia Medica.—The *dose* is 5 to 60 grains (0.3 to 4 Gm.).

⁂ *Potassii Bromidum* (U.S.P., B.P.).—KBr. Soluble in 1.6 water, 200 alcohol.

Sodii Bromidum (U.S.P., B.P.).—NaBr. Soluble in 1.2 water, 13 alcohol.

Ammonii Bromidum (U.S.P.).—NH_4Br. Soluble in 1.5 water, 30 alcohol.

Lithii Bromidum (U.S.P.).—LiBr. Soluble in 0.6 water, very soluble in alcohol.

Calcii Bromidum (U.S.P.).—$CaBr_2$. Soluble in 0.7 water, 1 alcohol.

* *Zinci Bromidum.*—$ZnBr_2$. Readily soluble.

Strontii Bromidum (U.S.P.).—$SrBr_2 + 6H_2O$. Soluble in 1.05 water, very soluble in alcohol.

* *Bromipin*, a combination of 10% of bromin and oil of sesame, is said to be more readily absorbed, to be less irritant, and less liable to produce bromism. *Dose:* 4 to 15 c.c. (1 to 3½ drachms) per day.

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* *Pulvis Potassii Bromidi Effervescens* (N.F.).—A heaped teaspoonful contains 0.6 Gm. (10 grains).

* *Pulvis Potassii Bromidi Effervescens cum Caffeina* (N.F.).—Contains, in addition, 0.06 Gm. (1 grain) Caffein.

* *Elixir Potassii Bromidi* (N.F.).—4 c.c. (1 drachm) = 0.6 Gm. (10 grains) KBr.

Acidum Hydrobromicum Dilutum (U.S.P., B.P.).—10%. *Dose:* 5 to 10 c.c. (1 to 2½ drachms), diluted.

VI. IODID ION.

With this the evidence is rather *clinical* than experimental.

The iodids are *specific in tertiary syphilis* and its sequels.[1] They also affect chronic rheumatism and asthma. They lead to the resolution of various pathologic formations, especially those involving connective tissue. They also produce obscure changes in metabolism, leading to marasmus and cachexia. The excretion of N is increased, but it occurs in less completely oxidized form. The same is true of sulphur. Iodin itself has a very similar action.

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[1] They were introduced for this purpose about the middle of the present century.

* Not official.

The most important preparations are marked ⁂.

If the actions of the iodid ion be studied more closely, it will be seen that there is comparatively little evidence of a true ion action, such as existed in the case of bromids. The effects are most easily explained on the *basis of salt action.* This is very strong in the case of iodids, and especially with KI. The cause of this is not difficult to understand, although it may be difficult to assign its proper place to each factor in individual cases.

1. Explanation of Action.—(1) Potassium iodid is *extremely diffusible* and penetrates very readily into the cells. (2) It contains practically two *foreign molecules*, one being entirely foreign. (3) The liberated iodid ion very likely combines with the proteids, to substitute itself for the chlorid. (4) The iodids are very easily decomposed, giving rise to free iodin or to hydriodic acid, both of which act as irritants, and both of which form another class of compounds with the proteids. (5) This combination with proteids serves to retain the iodin for a very long time in the body, so that its action is not only quick and profound, but also very lasting.

The *excretion* of iodin by the urine begins very early. It exists largely as organic iodin compounds. None can be demonstrated in the blood two days after the last dose. But it has not disappeared from the body at this time, for traces of it can be shown in the urine for twenty days, and considerably larger quantities are contained in the saliva and in other proteid containing secretions. The latter fact speaks very strongly in favor of the existence of *iodin-proteid combinations.*

The only compound of this kind which has so far been actually demonstrated is Iodothyrin (see p. 315). This cannot be formed by the action of iodin on thyroid substance outside of the body, but its quantity is increased when iodids are taken by mouth. After the administration of iodids, iodin can also be demonstrated in the kidneys, blood, alimentary canal, trachea, and bronchi, but not in the liver, brain, spleen, lung-tissue, or adipose tissue.

(6) The iodin excreted in this way into the alimentary canal is reabsorbed, and may make the circuit of the body several times and repeat its actions.

2. Iodism.—The liberation of free iodin and hydriodic acid, which are both strong irritants, may give rise to very unpleasant side-effects resembling in a general way those which were described as bromism—gastritis, various skin diseases, coryza, parotitis, etc. The iodids are very weak compounds and are decomposed even by carbonic acid. Since the latter is most abundant in the respiratory organs, these show a pronounced local action. The extent of the local manifestations of iodism varies greatly in different individuals, or in the same individual at different times; this may perhaps be explained by a different degree of acidity. They can be prevented very largely by the administration of alkalies.

3. Iodids on **intravenous injection** exert a quite characteristic action on the cardiac **vagus endings**, paralyzing them after the manner of atropin. They also lower the excitability of the depressor, so that stimulation of its trunk does not lower the pressure in the normal manner. In the frog, they cause rigor of the skeletal muscle. In rabbits they produce death through pulmonary edema with pleural effusions. The latter phenomena are probably due to the irritant action of liberated iodin.

4. Therapeutics.—1. Third Stage of Syphilis: The continued administration of iodids in this stage removes all the symptoms in a specific manner, arrests the progress of the disorder, and repairs the existing lesions.

It is impossible to say at present whether the iodids exert a specific action on the syphilis organism, if such exists, whether their effect is due to an ion action on metabolism, or whether it is simply a general salt action, the breaking down of pathologic new-formation. The iodids alone seem to have no action in the first and second stages of syphilis. But in the latter they are often useful in combination with mercury.

It makes no difference in this case whether one gives mercuric chlorid and potassium iodid or mercuric iodid; for the latter will be decomposed into mercuric chlorid, and its iodin will form sodium iodid.

The iodin also seems to aid in the removal of mercury which has been accumulated in the body during the first and second stages.

It seems to be similarly useful in the removal of lead in chronic lead-poisoning. It acts, perhaps, by stimulating the general activity of the cells, but the subject is very little understood.

2. Its action in **chronic rheumatism** presents the same problems, and it cannot be decided whether it acts by dea specific toxicity, so that the following description will be generally applicable.

Since the capacity for the excretion of these salts is greater than the capacity for their absorption, they do not usually develop their ion action when taken by the mouth. However, if introduced in strong solution they may cause necrosis of the lining membranes, and will then enter the circulation more rapidly, and produce the ion symptoms described under the several headings. Ordinarily their action is a purely local one, proportional to their concentration and to the time during which they remain in contact. The latter again is proportional to their quantity. Since the concentration is necessarily greatest at the points where they enter and leave the body, the irritation is most manifest in the alimentary canal and in the kidneys, producing gastritis, enteritis, and nephritis. The phenomena are the same as with other irritant poisons (see Chap. XXVIII, A). They consist in great abdominal pain, vomiting, frequently bloody stools; irregular pulse, convulsions, and collapse; suppression of urine, or that passed is albuminous and often bloody. The gastro-enteritis may be so violent as to lead to an early fatal ending. Of the salts so far studied, the potassium nitrate is by far the most violent; 30 Gm. (1 ℥) may be fatal if taken in concentrated form.

The *treatment* would consist first in dilution, since they act only by virtue of their concentration. Large quantities of water should be drunk and the stomach washed. Demulcents—milk, egg white, acacia—are also useful. The symptoms should be met as they arise.

IX. THE CHLORATE ION.

The chlorates display some peculiar ion actions.

They are strong oxidizers chemically, but do not exert this action in the body.

When the chlorates are added to blood, either inside or outside the body, they effect the *formation of methemoglobin*. The chlorate ion is not used up in this process, so that it may convert an indefinite amount of hemoglobin. They differ in this respect from the nitrites (see p. 476), and their action is in consequence more violent and more prolonged. They may in this way produce an actual asphyxia.

The blood of different animals shows a different degree of readiness for this methemoglobin formation. This is very frequent for all poisons acting on the blood, especially as between carnivorous and herbivorous animals. The cause is not understood, but is perhaps connected with differences in the alkalinity of the body. The conversion occurs fairly readily *intra vitam* in man, dog, and cat, whilst rabbits and guinea-pigs are almost immune. But in the test-tube chlorates convert rabbit's blood, although more slowly than dog's.

In addition to this formation of methemoglobin, the chlorates break up the *blood-corpuscles*. This was formerly supposed to produce dangerous embolism, but less importance is attached to it at present. But the proteids, etc., which are liberated by the destruction of the corpuscles are extremely irritant to the kidneys and produce a very marked *nephritis*, with the usual phenomena—proteids in the urine, casts, sometimes hemoglobin compounds. Possibly the chlorate ion itself irritates the kidneys.

The chlorates have also a *disinfecting and local stimulant action*, which seems to be rather stronger than would be accounted for by their salt properties, and would therefore appear to be specific ion actions.

The **toxicology** of potassium chlorate is fairly important. Poisoning very frequently takes place accidentally, either by an overdose, since the laity does not generally regard it as a toxic substance, or by the swallowing of some of the solution given for gargling.

The **symptoms** are those of a *gastro-enteritis*, as just described (p. 566). After its absorption, it produces symptoms due to the methemoglobin formation and destruction of corpuscles; *i. e.*, peculiar *cyanosis*, *nephritis*, hematuria, blood casts, possibly suppression of urine. Icterus is also common. If the action on the kidney is still stronger, uremic symptoms—coma and convulsions—may result. The course of poisoning may be very rapid. Death has taken place in two and a half hours. Usually, however, it does not occur for several days.

The **treatment** would be the same as for other irritant salts (see p. 566).

Therapeutics.—The local disinfectant and stimulant action to mucous membranes is alone important, and is extensively utilized in sore throat, a saturated solution being used as gargle. The patient should be cautioned against swallowing it. There would seem to be no indication for its internal use, and the popular tablets are to be condemned.

MATERIA MEDICA.

⁂ *Potassii Chloras* (U.S.P., B.P.), $KClO_3$.—Soluble in 16.7 water. Insoluble in absolute alcohol. *Dose:* 0.2 to 1.2 Gm. (3 to 20 grains). As a gargle, 1% to 5% solution.

Trochisci Potassii Chloratis (U.S.P.).—Each contains 0.3 Gm. (5 grains).

Trochiscus Potassii Chloratis (B.P.).—Each contains 0.2 Gm. (3 grains).

X. THE PERMANGANATE ION.

This is so readily decomposed into O and MnO_2 in contact with organic matter, that its action can never be anything but local. It is an irritant and disinfectant. Taken by the mouth in large dose it may cause death by gastro-enteritis.

The **Potassium Permanganate** (U.S.P., B.P.) ($KMnO_4$) is the only salt used. It may be taken in 1/3 % solution as antidote to organic poisons, HCN, and phosphorus. Its main use is as an antiseptic. It is so readily destroyed and so expensive that its use is not very extensive. 1 : 2000 to 1 : 500 solution may be used as injection in dysentery, in urethritis, or as mouth-wash. A saturated solution (1 : 16) may be used for the hands, the color being removed by a solution of oxalic acid. The MnO_2 into which it is decomposed is employed against chlorosis. For this purpose the *dose* is 0.03 to 0.1 Gm.

XI. ACETATES AND CITRATES.

The acetates and citrates have no peculiar ion action. They act just like other neutral salts; but, like the alkali salts of most organic acids, they are decomposed in the body with the formation of carbonates: $HC_2H_3O_2 + O_2 = 2CO_2 + 2H_2O$; so that they exert an alkaline action after their absorption. This alkali action is of special importance on account of the profuse diuresis which results from it. The citrates are not readily absorbed, and are therefore *cathartic.*

MATERIA MEDICA.

The *dose* of the salts is 0.3 to 4 Gm. (5 to 60 grains).

⁂ *Potassii Acetas* (U.S.P., B.P.).—Soluble in 0.36 water, 1.9 alcohol; deliquescent.

Sodii Acetas (U.S.P.).—Soluble in 1.4 water, 30 alcohol.

* *Elixir Potassii Acetatis*, N.F.—A teaspoonful = 0.3 Gm. (5 grains).

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* Not official.

The most important preparations are marked ⁂.

Potassii Citras (U.S.P., B.P.).—Soluble in 0.6 water, sparingly in alcohol; deliquescent.

Lithii Citras (U.S.P., B.P.).—Soluble in 2 water, sparingly in alcohol.

Liquor Potassii Citratis.—(U.S.P., B.P.) (Effervescent).—4 c.c. (1 drachm) = 0.36 Gm. (6 grains).

Potassii Citras Effervescens.—*Dose:* Heaping teaspoonful.

Lithii Citras Effervescens (U.S.P., B.P.).—*Dose:* Heaping teaspoonful.

* *Elixir Lithii Citratis,* N.F.—Teaspoonful = 0.3 Gm. (5 grains).

XII. CALCIUM.

The action of calcium *when injected* directly into the blood has not been extensively studied. It seems to resemble the actions of magnesium and potassium, producing a fall in blood pressure and paralysis of the central nervous system.

These actions do not appear when calcium salts are *taken by the mouth,* since these cannot be absorbed in sufficient amount. The small quantities which enter the body are excreted mainly through the intestine, in part also through the urine. This then becomes alkaline.

The **importance of the calcium** ion arises from the fact that it is a universal constituent of protoplasm, only a few of the lower fungi being able to dispense with it. It appears to be mainly fixed in the nuclei, while in the extranuclear portion its place seems to be taken by magnesium. It appears to be essential not only to the living protoplasm, but also to unorganized ferments (rennet, fibrin ferment, etc.; it is not, however, essential to all ferments—*e. g.*, pepsin digestion may go on in its absence).

Its importance to living protoplasm has already been discussed in connection with the general ion action (see p. 552). Similarly the toxic effects of oxalates and fluorids seem to be dependent upon a precipitation of calcium, and not upon any direct toxic action of the anion.

A more gradual withdrawal of calcium from the body, by withholding it from the food, leads in animals to effects which closely simulate those of *rickets and osteomalacia.* There is, however, some difference: In calcium starvation, but little bone is formed, yet this contains the normal amount of calcium. In rachitis, the amount of bone is even excessive, but it is very poor in Ca. In man these conditions are characterized by a diminished amount of calcium in the bones. The thought lay near at hand to employ calcium, particularly calcium phosphate, in the treatment of these diseases. The results have been somewhat disappointing, as might have been deduced from theoretic considerations. The condition is somewhat similar to that existing in chlorosis, for except in the experimental disease, the cause of the disorder is never to be found in insufficient supply of calcium salts, since the amount of these in the food is always more than enough to supply the demands of the organism. The real cause must be sought in the abnormal absorption or utilization of these ions.

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* Not official.

The essential nature of this abnormal process is not at present known. In diseases in which there is an abnormal formation of acid in the blood—*e.g.*, diabetes—the excretion of calcium and magnesium is increased, but no such diminished alkalinity exists in rickets. Even when we assume the cause to be a deficient absorption, this could not be remedied by additional introduction of calcium, for it is of course extremely unlikely that calcium would be more easily absorbed from such inorganic salts as phosphates, than in the form in which it exists in the food.

Calcium salts have also been given in *hemophilia* to increase the coagulability of the blood. Although the last word has not been spoken on this interesting subject, it would seem that hemophilia is not usually dependent upon the deficiency of lime salts. Nevertheless most clinicians report very favorable results. Further than this use, there would not seem to be any rational therapeutic indication for the calcium ion, the calcium salts only being useful on account of the acids with which they are combined, or by virtue of their alkaline action.

MATERIA MEDICA.

	Solubility in Water.	Dose: Metric.	Apothecaries'.
⁂ *Creta Preparata* (U.S.P., B.P.). (*Prepared Chalk, Drop Chalk.*) $CaCO_3$ . .	Insol.	0.5 to 4.0	10 to 60 grains.
Pulvis Cretæ Compositus (U.S.P.).	. . .	0.5 to 4.0	10 to 60 grains.
Pulvis Cretæ Aromaticus (B.P.) and *Pulvis Cretæ Aromaticus cum Opio* (B.P.)	. . .	. . .	. . .
Mistura Cretæ (U.S.P.)	. . .	8.0 to 15.0	2 to 4 drachms.
Trochisci Cretæ (U.S P.). Each contains 0.25 Gm. (4 grains) . .	. . .	. . .	. . .
Calcii Carbonas Præcipitatus (U.S.P., B P.). (*Precipitated Chalk.*).	Insol.	0.5 to 4.0	10 to 60 grains.

The most important preparations are marked ⁂.

	Solubility in Water.	Dose: Metric.	Apothecaries'.
⁂ *Liquor Calcis* (U.S.P., B.P.) (*Lime-water.*) A saturated solution of Ca(OH)$_2$, made by leaving freshly slaked lime in contact with water	. . .	4.0 to 30.0	1 to 8 drachms.
Syrupus Calcis (U.S.P.) [*Liquor Calcis Saccharatus* B.P.]. (A stronger solution of Ca(OH)$_2$ in Syrup)	. . .	1.0 to 4.0	15 to 60 minims.
⁂ *Calcii Phosphas Præcipitatus* (U.S.P.) [Calcii Phosphas, B.P.]. Ca$_3$(PO$_4$)$_2$	Insol.	0.3 to 2.0	5 to 30 grains.
Syrupus Calcii Lactophosphatis (U.S.P., B.P.)	. . .	4.0 to 8.0	1 to 2 drachms.
⁂ *Calcii Chloridum* (U.S.P., B.P.). CaCl$_2$. (Hygroscopic.)	1.5 parts.	0.3 to 1.2	5 to 20 grains.
Calx (U.S.P., B.P.). *Unslaked Lime.* Used as caustic and disinfectant	. . .	. . .	. . .
Calcii Hydras (B.P.). *Slaked Lime.* Used as disinfectant	. . .	. . .	. . .

XIII. BARIUM.

This element has very interesting *ion actions*, resembling those of most of the organic groups. This may possibly be due to their replacing calcium in the proteid molecule.

Besides its rather specific irritant action on the alimentary canal, it possesses a veratrin action on muscles, a digitalis action on the heart, a constricting action on the arterioles (directly muscular), and a stimulating and then paralyzing action on the central nervous system.

Its **local action** results in gastro-enteritis and some degree of corrosion, and fairly *large absorption.* It may, therefore, produce its **systemic actions** even when given by the mouth. The most conspicuous of these are upon the circulation: a slowing of the heart (digitalis action), a rise of blood pressure (constriction of arterioles). The pulse is, therefore, small, hard, and slow. Large doses paralyze the cardiac muscle.

When given in very dilute solutions the amount absorbed is very small, and is then *deposited in the bones.* The *fatal dose* of barium salts is given as 3 to 15 grains. The chemic antidotes are sulphates (Glauber's salt), which act by forming the insoluble barium sulphate. (Barium has no therapeutic indication.)

The most important preparations are marked ⁂.

XIV. STRONTIUM.

This resembles barium in its action, but is somewhat weaker. Being less corrosive, it does not enter the blood in sufficient amount to produce toxic action. In dilute solutions only very small amounts are absorbed from the stomach; none from the intestine, since it is converted into phosphates, in which form it is also generally deposited in the bones.

Strontium also possesses no therapeutic indication. It may be useful to moderate the action of anions, since its salts must be decomposed before the anions can be absorbed.

MATERIA MEDICA.

Strontii Lactas (U.S.P.).—Soluble in 4 parts water. *Dose:* 1 to 8 Gm. (¼ to 2 drachms).

XV. OXALATE ION.

Oxalic acid is quite a strong organic acid, and exhibits the ordinary acid actions. The oxalates act as soluble salts. In addition to this, however, they show an effect which must be referred to the oxalate ion. This consists of a specific **toxicity to all protoplasm.** The phenomena resemble in all respects those produced by HCN. The action is probably explained by the fact that the calcium is rendered insoluble.

In accordance with this theory, it is found that oxalates are not toxic to a few lower fungi which do not contain calcium. It is toxic to most plants, but certain species contain soluble oxalates. In algæ the main histologic changes are seen in the portions richest in calcium—nucleus and chlorophyll. Oxalic acid is probably a constant product of metabolism, and possibly one of the functions of calcium is to render it harmless.

If oxalates are **injected into the circulation** they affect first the *central nervous system* in its whole extent, from mental functions to reflexes, producing at first stimulation and then *paralysis*, the latter being the more conspicuous.

In consequence of the *asphyxia* produced in this manner they cause glycosuria, and possibly through the same cause indicanuria. *Death* occurs from respiratory paralysis, excepting when the poison is injected directly into the circulation, in which case it may paralyze the cardiac muscle.

Taken by the mouth, the oxalates are *readily absorbed*, and poisoning is not at all infrequent from confusion with other salts.

The **symptoms** are: first, those of a local caustic, especially when the acid was used; then those of collapse, the latter possibly preceded by convulsions. The pulse is very small and weak.

Almost the entire quantity is *excreted*, unchanged, by the urine (92% to 95% after hypodermic injections) in the form of calcium oxalate. This is almost insoluble and forms envelope-shaped crystals, which are diagnostic of oxalate-poisoning. The crystals may be excreted in such great amounts as to lead to blocking of the urinary tubules, and possibly to *nephritis*, or retention of urine and uremia from this cause. Calcium oxalate, in rod-shaped crystals, may be found in all the organs, but it may be absent from these in very acute poisoning.

Death by oxalic acid and oxalates occurs very rapidly, much more quickly than by any other caustic substance. This is of diagnostic importance. (In one case death took place in ten minutes.) The *fatal dose* will vary with the concentration. The smallest recorded amount is 5 grams.

The chemic *antidote* would be calcium in any shape, chalk, lime-water, etc. Liberal quantities of water should be given to prevent the deposition of crystals in the kidneys.

Oxalates have no therapeutic importance. They may occur in rather large amounts in some articles of food,—*e. g.*, spinach,—but not in such amounts as to be dangerous.

XVI. FLUORIDS.

Fluorids have a very strong *local irritant action.*

Their *systemic action* resembles that of oxalic acid, and is probably produced in the same manner, by the formation of insoluble calcium salts. In cases of poisoning the local symptoms are somewhat more pronounced than is the case with oxalic acid.

When fluorids are given in small amounts, greatly diluted, they are absorbed and *deposited* for the most part *in the bones.*

The bones become unusually hard, white, and brittle, and contain small crystals, presumably $CaFl_2$. A small amount of the latter is normally contained in the bones and teeth, but the percentage (0.02–0.05) is so small that it cannot be regarded as essential.

The fluorids are quite markedly *antiseptic.* In the proportion of 1 : 200 they prevent completely the development of bacteria, and are sometimes used for this purpose. They have no important therapeutic application, and small toxicologic importance.

* *Sodii Fluoridum* (Sodium fluorid), NaF.—Soluble in 25 parts of water. Used externally as antiseptic. For dressings, 0.5 to 10 : 1000; injections, 0.25 to 1 : 100; against fermentation in food, 10 to 15 : 100,000.

XVII. BORIC ACID AND BORATES.

The former possesses acid, the latter alkaline characters. Neither is very strong; nor indeed do they possess pronounced actions of any kind.

Boric acid is used as a mild *antiseptic*, in the form of dusting-powder or as saturated (4%) solution, or as Boroglycerite. It is less irritant than most other antiseptics. It has also been recommended for preserving food, in the ratio of 4 to 8 grains per pound.

Sodium borate is used as a *mild alkali* on the skin, or a mild laxative by the alimentary canal.

The use of boric acid as a preservative gives some practical importance to the question of any toxic effects. Sufficient could also be absorbed from wounds to produce general phenomena, if such existed.

Extremely *large doses* may cause acute collapse. This is, however, quite rare, the symptoms usually extending over several days and consisting mainly in subacute gastroenteritis, loss of appetite, nausea, vomiting and catharsis, laxative to purgative; on the part of the organs of excretion, nephritis and skin eruptions; on the nervous system, muscular debility, incoordination, fall of temperature, and finally collapse.

The autopsy shows fatty degenerations.

It appears to be absorbed fairly readily; its excretion occurs mainly by the urine, and is practically complete inside of twenty-four hours.

The above effects only follow excessively large doses—much larger than any which could be introduced with the food. Recent observations have demonstrated that amounts of Borax or Boric Acid as large as 3 to 5 Gm., in dogs, were absolutely devoid of effects upon utilization of food or upon metabolism, even when continued for some time. On account of the rapid excretion, there is absolutely no chance for a cumulative action.

* Not official.

No deleterious action has therefore been demonstrated for either borax or boric acid, in any quantities which would be likely to be used as food preservatives (up to 2.5 Gm. per day and continued indefinitely). They are probably the most harmless of these antiseptic substances. None the less, many authorities condemn their employment, basing themselves upon older experiments, now proven fallacious.

MATERIA MEDICA.

⁂ *Acidum Boricum* (U.S.P., B.P.) (*Ac. Boracicum*), H_3BO_3.—Soluble in 26 parts water, 10 glycerin, 15 alcohol. (Saturated aqueous solution = 4% = 17 grs. per ounce.) *Dose:* 0.3 to 1 Gm. (5 to 15 grains). As lotion, injection, or gargle, 2 to 4%; as ointment, 10 to 20%.

Unguentum Acidi Borici (B.P.).—10%.

⁂ *Glyceritum Boroglycerini* (U.S P.) [*Glycerinum Acidi Borici*, B.P.].—Contains 31% of Boric Acid. For external use. Diluted 10 times.

⁂ *Sodii Boras* (U.S.P.) [Borax, B.P] (*Sodii Biboras, Borax*), $Na_2B_4O_7 + 10H_2O$.—Soluble in 16 parts water, 1 part glycerin. *Dose:* 0 3 to 2 Gm. (5 to 30 grains).

Glycerinum Boracis (B.P.).—1 : 6.

Mel Boracis (B.P).

XVIII. URATES AND URIC ACID.

The importance of these lies in the fact that they may be formed or retained in excessive amounts in pathologic conditions, when they first produce inflammatory necrosis of cells, and are then deposited in insoluble granular form. This, becoming crystalline, acts as a powerful mechanical irritant, producing the phenomena of gout. These can be simulated in animals by the injection of suspensions of acid sodium urate.

The most important preparations are marked ⁂.

CHAPTER XXVI.

REMOTE (ION) ACTIONS OF ACIDS AND ALKALIES.

(A) ACTIONS COMMON TO BOTH.

1. Fourfold Action.—Acids and Alkalies exert a fourfold action:

1. By virtue of their *chemic* character, they produce, when fairly concentrated, profound changes in the body constituents, dead or living, and lead to destruction of tissue.

2. When dilute, they have an extensive and peculiar ion action upon the living protoplasm, due to the H and OH *ions*.

3. Like all other soluble and absorbable substances, they produce *osmotic* changes, and exert the ordinary salt action.

4. By influencing the action of ferments and the solubility of substances, they modify the processes of *digestion* and absorption.

The first, the purely chemic action, overshadows all others when strong solutions are applied. It will be studied in connection with corrosives in Chapter XXVIII.

The ion actions proper, the salt actions, and the effects upon digestion are most pronounced in dilute solutions, and these will be discussed in the present chapter.

2. Fate in Body.—Neither acids nor alkalies are absorbed unchanged from the alimentary canal. The alkalies (including the carbonates) are *neutralized* by the HCl of the gastric juice. Or if given in larger amounts, they enter into loose alkali-*proteid combinations* before they reach the blood. The acids undergo a similar change, or if they are not entirely absorbed before entering the intestine, they are there neutralized by the carbonates. The direct effects, then, would consist only in altering the reaction of the alimentary canal, and in a certain amount of salt action.

However, there are other changes—more remote, but very important: The compounds with the proteids still possess the character of acids or alkalies; and even when the neutralization is effected by the HCl or Na_2CO_3, it is evident that the total amount of alkali in the body must be altered, at least temporarily. But since the organism is adjusted to work at a certain degree of alkaline reaction, which cannot be departed from without more or less severe modifications in its function, it endeavors to counteract these changes in reaction. A *regulating mechanism* for this exists in the *formation of ammonia*. This is normally produced as a precursor to urea; but the degree to which the final transformation takes place is easily modified by increasing or diminishing the fixed alkali of the blood. In the former case it is more complete; whereas if acid is introduced, the transformation does not take place, but the ammonia is excreted unaltered as a salt of this acid. It is therefore evident that acids and alkalies must influence the proportion of nitrogen which is excreted as ammonia and as urea. It is not inconceivable that this change introduces other modifications in the metabolism, but nothing is known about this.

If the ammonia formation is not sufficient to cope with the excess of acid or alkali, another mechanism for the maintenance of the normal reaction of the organism exists in the *rapid excretion* of any excess by the urine, in the form of acid or basic salts. (Free acids or alkalies never exist in the body beyond the alimentary canal.) Acids and alkalies are therefore very efficient *diuretics*.

On account of these mechanisms it is possible to give very large amounts of acids or alkalies to animals, by the mouth, without greatly altering the alkalinity of the blood.[1] Their efficiency, especially against acid, is, however, not the same for all animals, and is conspicuously more perfect in carnivora—probably because these are accustomed to ingest a certain amount of acid with their food. It is absolutely impossible to lower the alkalinity of the blood of a dog, to such a degree as to produce symptoms, by introducing acid into the alimentary canal, unless corrosion be produced. But if an acid be injected into a vein, it will cause very pronounced symptoms, and these may also be produced in herbivorous animals if large quantities are given by the mouth. They will result in death even before the reaction of the blood has become neutral. So that it is not strictly correct to speak of an "acid action," but rather of the effects of diminished alkalinity.

3. (a) These **acute effects of acid injection**—*i. e.*, of

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[1] The alkalinity of the blood is most conveniently estimated by the CO_2 which it carries.

diminished alkalinity of the blood[1]—fall upon the central nervous system, especially the medullary centers, and are mainly paralytic. There are coma, convulsions, depressed respiration and fall of blood pressure, etc. Death takes place by respiratory paralysis. These symptoms are at once removed—even in the last stages—by injection of Na_2CO_3. This, as well as the fact that the serum in acid-poisoning is never saturated with CO_2, shows that the cause of the fatality of diminished alkalinity is not due to the incapacity of the blood to take up the CO_2 formed in the tissues. The formation itself is diminished.

(b) **Diabetic Coma.**—These phenomena bear the closest resemblance to those of diabetic coma. Experimental investigation has, indeed, shown that the excretion of ammonia in this disease is always markedly increased, pointing to the presence of an abnormal amount of acid in the body.[2] This is oxybutyric acid; according to some, this again is formed from β-amidobutyric acid. As to the origin of the latter, but little is known. It could be derived either from fat or proteids. The theory lay near to refer the phenomena of diabetic coma to acid-poisoning. Against this it was urged that the amount of this acid in the urine was insufficient to account for the symptoms. But plainly, it is not the excreted acid, but that retained in the body, which would be responsible for the effects; and it is claimed that recent calculations have shown that the alkalinity of the body is diminished to such a degree as to suffice for the explanation of the symptoms.

The rational *treatment*, then, for this condition would be the administration of alkali in sufficient quantity, just as in the case of acid-poisoning in the rabbit. When this has been done in the proper manner the results have been brilliant. The principal difficulty has been that a sufficient amount of alkali was not used. If the alkali is administered by the mouth, in the early stages before coma sets in, it should be given in a dose of about 40 grams of sodium carbonate a day; and if coma has already set in, the quantity should be 100 or 200 grams. Carlsbad salt is also useful in this connection.

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[1] The *alkalinity of the blood*, as well as its CO_2, is also lowered by phosphorus, arsenic, and other metals, and in diabetes. It is increased in pregnancy, as also by salts of organic acids, which may be contained in the diet.

[2] It must not be supposed that an increase of ammonia in the urine always indicates an increased formation of acid. It may as well be due to changes preventing the ultimate steps in nitrogenous metabolism, *e. g.*, in hepatic diseases.

If such large quantities of sodium carbonate are taken, they will produce a cathartic effect. This purging may not be entirely useless, for it is conceivable that the underlying cause of the diabetes is found in toxins formed in the alimentary canal. At all events, plain purges have been found useful in such cases, and so has pilocarpin, used on the theory that it helps the elimination of the "toxins." But if catharsis occurs after sodium carbonate, so much may pass into the stools that it may be impossible to secure the absorption of a sufficient amount of alkali. In this case it should be given by intravenous injection of 0.3 % solution of the crystallized salt. (Hypodermic injection is apt to cause sloughing.)

It will not do to wait with the administration of the alkali until the coma actually sets in, for it may then be too late. Diabetic coma differs in this respect from the acid-poisoning in the rabbit. The reason is, that in the latter the diminished alkalinity exists mainly in the blood, and may be readily influenced by the injected alkali; whereas in diabetic coma the acid is formed inside the cells, into which the alkali penetrates with more difficulty.

4. General Effect upon Metabolism.—The effects of *lesser changes in the reaction of body tissues* must be rather limited, since these are so promptly brought back to normal. Whilst it cannot be doubted that such changes must have an influence upon metabolism, the nature of this cannot be stated, because it is complicated by the actions of these substances on the alimentary canal. The latter is different in the case of acids and alkalies. Some of the other actions also require separate consideration. *Organic Acids* and their salts are rapidly burned to carbonate after their absorption (see p. 568); so that they act as acids only in the alimentary canal, but as alkalies after they are absorbed.

(B) EFFECTS OF DILUTE SOLUTIONS OF ACIDS.

1. On the Alimentary Canal.—**(a) Mouth.**—Acids have a characteristic "*sour*" *taste*, and are slightly astringent in the mouth. This taste determines their use as flavors (see p. 125).

It is one of the principal elements in the taste of wines, fruits, etc.

The addition of acid also makes it possible to take much larger quantities of cold water than could be taken without. They are therefore of therapeutic value in *fevers*, when one wishes to obtain at the same time the refrigerant action of cold and the diuretic effect of large quantities of fluid. They soften the enamel of the *teeth*, and should therefore be taken by means of a glass tube.

They also reflexly increase the flow of *saliva*, but this is of little practical importance.

(b) In the **stomach** their importance lies in the fact that *pepsin* cannot act except in the presence of acids. While any acid may answer for this purpose, hydrochloric seems to be the best, and is most efficient in the concentration existing in the gastric secretion; it also aids in the *solution of the connective tissue* of meats; and it determines the *antiseptic* qualities of gastric juice.

(c) **Intestine.**—Acids increase reflexly the flow of *pancreatic juice*. If free acid penetrates into the intestinal canal it acts as a very powerful irritant and produces increased *peristalsis*. Acids given by the mouth, however, are usually absorbed before passing the pylorus, so that this cathartic action is seen practically only when acids are generated in the intestine itself. There are, however, certain difficultly soluble acid salts, such as potassium bitartrate (cream of tartar), which are not dissolved in the stomach, and which may therefore extend their acid action to the intestinal canal. These acid salts are more strongly cathartic than ordinary salts in the same conditions.

2. **On Urine.**—Acids are markedly diuretic; this is in part a salt action, in part due to the H ion. The urine will become more acid (due to acid salts, not to free acids). This leads to an *increased irritability of the mucous membranes* of the urinary passages, so that inorganic acids are to be avoided in all inflammatory conditions of these organs. They must also be avoided where there is a tendency to the formation of uric acid *calculi*. It may be repeated that they increase the ammonia of the urine at the expense of the urea.

3. **Effects upon Metabolism.**—Outside of this change in the ratio of ammonia and urea, these are quite small, as far as our present means allow us to judge. The excretion of nitrogen seems to be pretty constantly slightly increased.

Applied directly to *excised organs*,—muscle, nerve, etc.,—the result is an increase and subsequent diminution of function.

4. Therapeutic Uses of Dilute Acids.—Their importance as flavors and for the introduction of cold liquids—the latter preferably as lemonade—has received mention.

The *diuretic action* cannot be utilized, since they are too irritant.

They are extremely useful in cases of *dyspepsia* in which an insufficient amount of acid is secreted. Hydrochloric and nitro-hydrochloric acids are preferred for this purpose, and these act best when combined with bitters. They would be contraindicated in catarrhal conditions, in which there is a hypersecretion of mucus. Even in normal individuals the prolonged administration of large quantities of acids is apt to prove too irritant, and interferes with digestion. This is the explanation of the popular use of vinegar to reduce *obesity*. A direct limitation of diet would seem a more rational means for this purpose.

The increased flow of pancreatic juice, and perhaps also of bile, which has been ascribed to acids, is probably too small to be of any value.

The *increase of peristalsis* produced by acid salts is of considerable importance. It may be obtained by cream of tartar. This has the advantage over the ordinary cathartics in that smaller doses suffice, nor is its taste as disagreeable.

Their use in *fevers* depends partly upon the diuresis and diaphoresis due to the increased introduction of liquid. It is also claimed that the alkalinity of the tissues is raised in febrile conditions, and that this is counteracted by acids. Phosphoric acid in large doses (10 Gm. diluted with 300 c.c. water) is said to depress the heart and slow the pulse, but would have no advantage over aconite for this purpose.

5. Materia Medica of Acids.—

(A) Summary.

(The small letters following the name of the acid refer to the more detailed description (pp. 583 to 587). The numbers refer to the brief description of the acids, given on page 583.[1])

Acids may be divided into inorganic and organic.

The inorganic acids, again, into *Hydracids*, containing the element in combination with hydrogen.
Oxyacids, containing oxygen.
Anhydrids, which yield true acids only after taking up H_2O.

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[1] The strong mineral acids are incompatible with organic substances and with each other.

TABLE XVI.—IMPORTANT INORGANIC ACIDS.

I. Inorganic. (These are all soluble in water or alcohol.)

		B.P	U.S.P.	
		Per Cent. of Pure Acid by Weight.	Per Cent. of Pure Acid by Weight.	Specific Gravity.
Hydracids.	*Acidum Hydrochloricum* (a), HCl (2, 4) (see below)	31.79	31.9	1.163
	⁂ *Acidum Hydrochloricum Dilutum* (3, 4)	10.58	10.0	1.050
	Acidum Hydrocyanicum Dilutum, HCN (1, 4)	2.00	2.0	. . .
	Acidum Hydrobromicum Dilutum (b), HBr (1, 3, 4)	10.00	10.0	1.077
	Acidum Hydriodicum, HI (a) (1, 4) In form of Syrupus Acidi Hydriodici.	. . .	1.0	. . .
	Acidum Hydrosulphuricum, H_2S (1, 4)	. . .	. . .	. . .
	⁂ *Acidum Nitricum* (d), HNO_3 (2, 4)	70.00	68.0	1.414
	Acidum Nitricum Dilutum (3, 4)	17.44	10.0	1.057
	Acidum Nitrohydrochloricum (e) (2)	. . .	. . .	. . .
	⁂ *Acidum Nitrohydrochloricum Dilutum* (3, 4)	. . .	. . .	. . .
Oxyacids.	*Acidum Phosphoricum* (f), H_3PO_4 (2, 4) (Concentratum, B. P.)	66.30	>85.0	>1.710
	Acidum Phosphoricum Dilutum (3, 4)	13.80	10.0	1.057
	Acidum Sulphuricum (g), H_2SO_4 (2, 4)	98.00	>92.5	>1.835
	Acidum Sulphuricum Dilutum (3, 4)	13.65	10.0	1.070
	Acidum Sulphuricum Aromaticum (3)	13.80	20.0	. . .
	Acidum Hypophosphorosum Dilutum, HPH_2O_2 (1, 3, 4)	Not official.	>10,0	>1.046
	⁂ *Acidum Boricum*, H_3BO_3 (1, 5)	. . .	. . .	. . .
Anhydrids.	*Acidum Arsenosum*, As_2O_3 (1, 5)	. . .	. . .	. . .
	" *Chromicum* (h), CrO_3 (2) (Yellow solid.)			
	Acidum Sulphurosum (i) SO_2 (1, 4)		>6.4	>1.035

II. Organic Acids.

Those of the Fatty Series are alone available for their acid character. (It will be recalled that this exists only locally, but disappears on their absorption. They are all soluble in water, with the exception of Oleic and Stearic Acids.)

The most important preparations are marked ⁂.

(*A*) *Acids of the Fatty Series.*—The official acids belong to the following chemic groups:

- *1. Monobasic Acids*, $C_nH_{2n+1}CO_2H$.
    - *Acidum Aceticum* (k), $HC_2H_3O_2$ (U.S P., 36%) (2, 4) [B.P., 33%].
    - ⁂ *Acidum Aceticum Dilutum* (U.S.P., 6%) (3, 4) [B.P., 4.27%].
    - *Acidum Aceticum Glaciale*, > 99% (2, 4) (U.S.P., B.P.).
    - * *Acidum Trichloraceticum*, $HC_2Cl_3O_2$ (2, 5).
    - * *Acidum Formicum* (l), HCO_2H.
    - *Acidum Stearicum* (m), $HC_{18}H_{25}O_2$ (1, 2, 5).
- *2. Dibasic Acids*, $C_nH_{2n}(CO_2H)_2$.
    - *Acidum Oxalicum* (n), $H_2C_2O_4 + 2H_2O$ (1, 5).
- *3. Oxymonobasic Acids*, $C_nH_{2n}(CO_2H)(OH)$.
    - *Acidum Lacticum* (o), $HC_3H_5O_3$, 75% (2, 4) (U.S.P., B.P.).
- *4. Dioxydibasic Acids*, $C_nH_{2n-2}(CO_2H)_2(OH)_2$.
    - *Acidum Tartaricum*, $H_2C_4H_4O_6$ (5) (U.S.P., B.P.).
- *5. Oxytribasic Acids*, $C_nH_{2n-2}(CO_2H)_3OH$.
    - ⁂ *Acidum Citricum* (p), $H_3C_6H_5O_7 + H_2O$ (5) (U.S.P., B.P.).
- *6. Monobasic Acrylic Acids*, $C_nH_{2n-1}(CO_2H)$.
    - *Acidum Oleicum* (q), $HC_{18}H_{33}O_2$ (1, 2). Brownish Liquid (U S.P., B.P.).

(*B*) *Composition of Acids of the Aromatic Series.* (These are never used for their acid character.)

(C_6H_6 = Benzol.)
$C_6H_5.CO_2H$ = Benzoic Acid. $C_6H_5.OH$ = Carbolic Acid.
$C_6H_4(CO_2H)_2$ = Salicylic Acid. $C_6H_3(OH)_3$ = Pyrogallol.
$C_6H_2(CO_2H)_4$ = Gallic Acid.
$2(HC_7H_5O_5) - H_2O = HC_{14}H_9O_9$.
Gallic Acid. Tannic Acid.

III. Acid Salts.

⁂ *Potassii Bitartras.—Cream of Tartar.*—$KHC_4H_4O_6$. Soluble in 201 parts of water. *Dose:* Diuretic, 1 to 3 Gm. (15 to 45 grains); purgative, 4 to 15 Gm. (⅛ to ½ ounce).

Brief Description:

(1) Not used therapeutically as acids.
(2) Used only externally.
(3) *Dose:* 0.1 to 1 c.c. (1 to 15 minims). Diluted in half a tumbler of water, best taken through a glass tube.
(4) Colorless liquid.
(5) Colorless or white solid.
(6) All the U.S.P. dilute acids contain 10%, with the exception of Acetic (6%), Hydrocyanic (2%).

(B) Details.

(a) *Acidum Hydrochloricum* (Muriatic Acid): *Prepared* by heating NaCl and H_2SO_4 and dissolving the gaseous HCl thus formed in water. The crude acid is obtained as a by-product in chemic industry. The strong acid gives fumes when brought near ammonia, or even in the air, due to the formation of NH_4Cl.

The *commercial acid* (strength = 30% to 33%) has a golden yellow color due to Fe and free Cl. Since it often contains As, it should not be used in internal medicine.

* Not official.
The most important preparations are marked ⁂.

(b) *Acidum Hydrobromicum Dilutum:* Prepared by decomposing $BaBr_2$ with H_2SO_4. It has been used as a nervous sedative, but its usefulness as compared with potassium bromid is more than doubtful. The acid sometimes acquires a yellow color, due to the liberation of Br. It should not be employed in this condition.

(c) * *Acidum Hydriodicum:* On account of its ready decomposition, this acid is never kept as such, but in the form of *Syrupus Acidi Hydriodici.* This is made by decomposing KI with Tartaric Acid. The keeping qualities are improved by the addition of Potassium Hypophosphite. The syrup keeps better in direct sunlight. It is used for its iodin rather than for its acid qualities.

(d) *Acidum Nitricum:* Made by decomposing $NaNO_3$ by H_2SO_4 and distilling the product.

The official concentrated acid is colorless, emits fumes of hyponitrous acid when exposed to air, and acquires a yellow color. It stains organic matter yellow; this is changed to orange by alkalies.

Important are also:

* *Acidum Nitricum Technicum:* Commercial Nitric Acid (Aqua fortis), 60% to 64%.

Acidum Nitricum Fumans: Almost absolute HNO_3 saturated with NO_2.

The concentrated acid is used as a caustic (glass rod); against hyperhydrosis of feet (1 to 2 oz. to pail of water); as disinfectant (will corrode metal vessels or pipes!).

(e) *Acidum Nitrohydrochloricum* (Nitromuriaticum) (U.S.P., B.P.) (Aqua Regia): Made by mixing 1 volume concentrated HNO_3 with 4.5 volumes HCl in an open vessel and allowing the mixture to effervesce. The composition is somewhat variable, but the final product contains NOCl and Cl_2 besides the two original acids. It is therefore a very powerful solvent and oxidizer.

The *dilute* acid is made by diluting the above with 3½ volumes of water. That of the British Pharmacopœia is somewhat more dilute. On account of the free chlorin, it may be supposed to have a stronger local irritant action than HCl. It is popularly supposed to "stimulate the liver," but its action does not differ in kind from that of other acids.

(f) *Acidum Phosphoricum:* Phosphoric Anhydrid (P_2O_5) forms three acids:

$$P_2O_5 + H_2O = H_2P_2O_6 = 2(HPO_3) = \text{Metaphosphoric Acid.}$$
$$P_2O_5 + 2H_2O = H_4P_2O_7 = \text{Pyrophosphoric Acid.}$$
$$P_2O_5 + 3H_2O = H_6P_2O_8 = 2(H_3PO_4) = \text{Orthophosphoric Acid.}$$

The last is the one official. It forms three series of salts; thus,

NaH_2PO_4, acid sodium phosphate.
Na_2HPO_4, neutral sodium phosphate.
Na_3PO_4, basic sodium phosphate.

It is prepared by burning phosphorus, dissolving the oxids in water, and completing the oxidation with HNO_3.

Phosphoric acid is said to be less detrimental to digestion than other acids; the evidence for this statement is rather weak.

(g) *Acidum Sulphuricum:*

Preparation.—The commercial ("English") Sulphuric Acid is made on a large scale by burning pyrites (impure iron sulphid) or native sulphur. The SO_2 is oxidized by means of nitrous fumes produced by the action of concentrated H_2SO_4 on Chili saltpeter ($NaNO_3$). The product is condensed in a system of leaden chambers in the presence of steam, and concentrated first in leaden pans and then distilled from glass or platinum retorts. This commercial acid is apt to contain Arsenic, and is therefore not to be used in medicine until further purified.

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* Not official.

Characters.—The official acid is an oily, colorless liquid, acquiring a brown color if exposed to dust. Very intensely corrosive, charring organic substances. Miscible in all proportions with water or alcohol, under the evolution of much heat. (Such mixing must be done very cautiously by slowly pouring the *acid into the water*, under constant stirring.) It has a specific gravity of 1.835, and boils at 338° C., distilling without decomposition.

Uses and Dose.—As other inorganic acids. Very frequently used for the liberation of gases (SO_2, H_2S, etc.), for which purposes it is best diluted with 4 volumes of water. It is also used for filling the porous cup in Daniel batteries (diluted with 8 volumes of water).

The * *Commercial Sulphuric Acid* (Oil of Vitriol) is very apt to contain Arsenic, and should not be employed in medicine.

Aromatic Sulphuric Acid is a mixture of H_2SO_4 and alcohol, containing ethyl-sulphuric acid. It is doubtful whether it possesses any advantage over other acids.

(h) *Acid Chromicum:* Chromic Acid, Chromic Anhydrid. CrO_3. Made by decomposing Potassium Bichromate with Sulphuric Acid and crystallizing: $K_2Cr_2O_7 + H_2SO_4 = K_2SO_4 + H_2O + 2CrO_3$. Very soluble in water; decomposes all organic liquids, often with explosion. Melts at 192° C. Used only externally as an astringent irritant (1% to 15%), or concentrated as a caustic. Also used against sweating feet (5% solution).

(i) *Acidum Sulphurosum:* Sulphurous Acid. A solution containing at least 6.4% of Sulphur Dioxid (SO_2).

Preparation.—Sulphuric Acid is made to act upon charcoal, and the SO_2 is dissolved in water. (For small quantities, extemporaneously, it suffices to act on Na_2SO_3 with H_2SO_4.)

It must be kept in small glass-stoppered amber-colored bottles.

Character.—Colorless liquid of characteristic odor.

Uses.—As antiseptic in skin and parasitic disease, etc. Against gastric fermentation 1 c.c. (15 ♏), diluted.

SO_2, generated by the combustion of sulphur, is a favorite disinfectant for rooms.

* *Acidum Osmicum:* OsO_4. Used only in histology for fixing tissues.

(k) *Acidum Aceticum:* Acetic Acid. $C_2H_3O_2H$.

Acid. Acetic. Glaciale: Glacial Acetic Acid. Nearly or quite absolute Acetic Acid. Congeals at somewhat below 15° C.

Acidum Aceticum: Acetic Acid, of a strength of 36% by weight. This corresponds approximately to the No. 8 acid of commerce.

Acid. Acetic. Dil.: Dilute Acetic Acid. Made by mixing 100 Gm. of Acetic Acid with 500 Gm. of distilled water. It contains 6% by weight.

* *Acetum:* Vinegar. A dilute impure acetic acid, of a strength of 6%, obtained by the fermentation of vinous liquors. That made by the "rapid process" from dilute alcohol is the one preferred in medical practice, but those obtained from wine, cider, etc., are also employed by the laity. Vinegar serves the same purposes as dilute acetic acid, but is inferior to it in keeping qualities.

* *Acetum Pyrolignosum:* Pyroligneous Acid, Wood-vinegar. A product of the destructive distillation of wood, containing 5% to 7% Acetic Acid, some Methyl-alcohol, Acetone, and Tar.

Used externally to combine effects of acetic acid and tar.

Preparation of pure *Acetic Acid:* Distillation of Sod. Acetate with Sulphuric Acid.

Preparations.—Besides those mentioned above, dilute Acetic Acid is used as a solvent in the class of aceta.

The dilute Acetic Acid is also often flavored with aromatics (Acid. Acet. Aromat., Ph.G.).

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* Not official.

Dose:

Internally, Ac. Acet. Dil.: 5 to 10 c.c. (ʒj to iiss).
Externally and for gargles, dilute 1 : 6 (= 1%).
Against corns, 36%.
In proportion of 1% is frequent addition to hair washes.

Acidum Trichloraceticum: $C_2Cl_3O_2H$. Prepared through oxidation of chloral. Used in substance or strong solution as a caustic; especially against warts; it is less painful than nitric acid.

(l) * *Acidum Formicum: Formic Acid*, HCO_2H.

Formic acid, as official in Germany and Switzerland, contains 25% of the absolute acid. It is prepared by the action of oxalic acid on glycerin.

It is used only externally as a counterirritant in the form of

* Spiritus Formicarum:

Formic Acid, 25%	2
Alcohol	35
Water	13

(Formerly prepared by macerating ants in alcohol.)

(m) *Acidum Stearicum:* Stearic Acid, $C_{18}H_{36}O_2$.

Preparation.—The official acid is the ordinary more or less impure commercial form, obtained by the decomposition of fats, especially tallow, with acid, either directly or after previous saponification, and separating the more liquid portion (Oleic Acid) by expression.

The solid product contains, besides stearic, also palmitic and other similar fatty acids.

Characters.—A hard, white, odorless and tasteless solid, soluble in alcohol and more readily in ether, melting at a temperature not lower than 56° C.

Uses.—To give consistency to salves and cerates.

(n) * *Acidum Oxalicum:* Oxalic Acid, $C_2H_2O_4 + 2H_2O$.

Preparation.—(*a*) By the action of HNO_3 on sugar or starch, or (*b*) by fusing sawdust with a mixture of KOH and NaOH. For medicinal use it is purified by recrystallization.

Characters.—Small, colorless and odorless, very acid crystals. Soluble in 10 parts water or 2.5 parts alcohol. It is bibasic.

Uses.—Acts as a caustic, but should not be used, on account of its toxic action after absorption. It is mainly of importance on account of its toxicology, having often been taken in mistake for $MgSO_4$, etc. The chemic antidotes are lime-preparations (chalk).

(o) *Acidum Lacticum:* Lactic Acid, $HC_3H_5O_3$. 75%.

Preparations.—Invert sugar is subjected to lactic fermentation in the presence of zinc oxid. The zinc lactate thus formed is decomposed by H_2S, and the filtered solution is evaporated to the required degree.

Characters.—Syrupy, intensely acid, colorless, and odorless liquid. Miscible with water, alcohol, or ether.

Uses.—Caustic, especially for dissolving diphtheritic membranes (1 : 5). There are no indications for its use internally.

(p) *Acidum Citricum:* Citric Acid, $C_6H_8O_7 + H_2O$ (tribasic).

Citric Acid is widely distributed throughout the vegetable kingdom, occurring either free or combined with K, Ca, or Mg. It exists in largest quantity in acid fruits of all kinds, usually along with Malonic and Tartaric and other vegetable acids.

Lemon juice is allowed to ferment, during which process the gummy matter precipitates. The proteids are removed by boiling, and the filtered juice is treated with chalk. The calcium citrate is decomposed by H_2SO_4, and the citric acid separated by crystallization.

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* Not official.

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Lemon juice contains 6% to 8% of the acids.

A large lemon contains about 4 Gm.

A 5 : 1000 solution makes the ordinary lemonade.

Externally it has been used in 10% to 20% solution to dissolve diphtheritic membranes.

An important use is against scurvy.

⁂ *Syrupus Acidi Citrici*, 1%. *Dose:* 5 to 20 c.c. (ʒj to iv).

(q) *Acidum Oleicum:* Oleic Acid, $C_{18}H_{34}O_2$.

Preparation.—An impure acid made by separating the liquid portion of the commercial acid after cooling to 5° C. This commercial acid is obtained as a by-product in the manufacture of stearin candles.

Characters.—A yellowish oily liquid, of a lard-like odor and taste; specific gravity, 0.900; insoluble in water, soluble in alcohol, ether, and solvents of fats; becomes semi-solid at 4° C.

Uses.—Pharmaceutically in the preparation of the oleates (see p. 69); also in plasters and soaps.

(C) EFFECTS OF DILUTE ALKALIES.

1. On the Alimentary Canal.—(a) Soluble Alkalies.—By virtue of their salt action and their chemic nature, alkalies will produce an *irritation* of the mucous membrane of the stomach. Their local action cannot extend beyond this organ, since they are neutralized. This irritation will be stronger or milder—and accordingly harmful or useful—according to the concentration of the alkali and the amount introduced. A mild degree of irritation will reflexly increase the *flow of gastric juice* and also lead to a more efficient *absorption*, as in the case of plain salt action. The process of absorption will, in addition, be favored by a solution of the *mucus* which forms a lining to the walls of the viscus—mucin being more soluble in alkalies. The activity of the *pepsin* of the gastric juice will be reduced by them.

(b) On the Intestine.—On the other hand, they will reduce the acidity of the chyme, and thus increase the alkalinity of the intestine, even if they are themselves neutralized and absorbed before reaching the duodenum. In this way they may favor the emulsification of *fats*, and the action of the *pancreatic ferments* if there is not sufficient alkali in the intestine. The *insoluble alkalies*—calcium carbonate—would have less action in the stomach and more in the intestine.

(c) It is evident that these effects would offer *no advantage in* **normal conditions.** Experiments show that whilst small doses of alkalies have no effect upon the utilization of food, large amounts lessen it. It is to be presumed that the normal amount of mucous coating in the stomach supplies a needed protection; the neutralization of the HCl would practically end gastric digestion; and the normal acidity of the chyme is not sufficient to interfere with intestinal digestion, and indeed supplies a useful stimulus to the secretion of pancreatic juice. The neutralization of the gastric juice also destroys its bactericidal action. (Indoxyl may be caused to appear in large quantities in the urine of a normal individual by a liberal administration of chalk.)

(**d**) But the facts are very different in **pathologic conditions**; *i. e.*, when there is a hypersecretion of mucus—as in gastric catarrh—or a hyperacidity as the result of fermentation. The former may line the gastric wall with a coating alike impermeable to the digestive secretions and products, and this the alkali will remove; whilst too great a percentage of free acid will cause severe and harmful irritation and interference with the action of ferments.

2. **Effects upon the Secretion of Urine.**—The *secretion of urine is increased* by all alkalies. This is due partly to the salt action, which is especially large since the alkalies possess a conspicuous penetrating power. In addition, one must also assume an ion irritation.

Precisely the same effect can be secured by the administration of salts of the *organic acids*, especially citrates or acetates, and this without causing any gastric disturbance, which latter may interfere with the administration of alkalies. The acetates are preferred, since they are the least cathartic of these organic salts.

The diuresis also increases the absolute amount of *all salts* excreted, although their percentage is, of course, lessened. The alkalinity of the urine is increased by an excess of basic salts. The urine is, in consequence, *less irritating* to the mucous membranes with which it comes in contact, and, at the same time, it is mildly stimulant.

To secure this alkalinity 7 Gm. of sodium carbonate or 15 Gm. of sodium acetate or citrate are required per day.

3. **Effects on Metabolism.**—On account of the importance of the alkaline reaction of the tissues for their functions, it might be expected that any modification of this alkalinity would profoundly modify the general metabolism. It was formerly supposed that the alkalinity caused an increased oxidation, but this is not supported by any direct evidence.

As has been pointed out, the change in reaction can only be very brief, and it is apparently not large enough, or not of such a nature, as to be demonstrable by our present methods. The actual results in regard to the total excretion of nitrogen are somewhat variable, but, on the whole, negative.

They are certainly not greater than might be expected from the pure salt action, or from the interference with digestion which would result from large doses. (Doses as large as 13 Gm. sodium carbonate, 20 Gm. of sodium bicarbonate, or 40 Gm. sodium citrate do not influence the total nitrogen excretion.)

The proportion of the urea-nitrogen is increased at the expense of the ammonia.

As to any increase or decrease of *uric acid*, this has not at the present time been sufficiently demonstrated. The effect upon carbon metabolism is equally small and uncertain.

The benefit of *citric acid in scurvy* is purely an empirical result, for which there is at present no explanation.

4. **Effect on Mucus.**—Mucin is more soluble in alkaline media, so that the alkalies dissolve any accumulations of mucus or render them more fluid. At the same time they increase mucus-secretion through an irritant and ion action.

5. The application of alkalies to **isolated organs,** muscles, nerves, etc., usually results at first in an increase and then in a diminution of function.

6. **Therapeutic Uses of Alkalies.**—**(a) Digestion.**—In catarrhal conditions alkalies would be useful throughout the alimentary canal by *dissolving the mucus* which lessens the permeability of the walls of these organs, preventing at once the pouring out of digestive juices and the absorption of the digestive products. It forms a similar impermeable coating about the masses of food. Further, the mere presence of a large amount of indigestible material—and tenacious mucus must be regarded as such—is in itself irritating.

In addition to this solution of mucus, the alkalies may be useful in counteracting the irritant effects of *excessive acidity.* The amount of acid normally present in the alimentary canal must be considered as the best condition for it. A slight temporary increase in this is of no importance, but if the acidity, especially of the intestine, is kept permanently high, a chronic irritation is set up, and leads to *gastro-intestinal catarrh.* Such a permanent increase of the acidity may be caused by acid articles of diet,—*e. g.*, sour wines, etc.,—or it may be the result of fermentative processes. A rather rapid formation of acids leads in this way to the *summer diarrhea* of infants.

When the acid is introduced from without, the principal indication is, of course, to put a stop to its introduction ; if it is formed in the intestine, to neutralize the already-formed acid and to remove the means of its formation, so as to prevent its recurrence.

If the hyperacidity is in the *stomach*, it may be neutralized by any of the soluble alkalies, sodium bicarbonate being the most useful. If it is in the intestine, the soluble alkalies will not be advisable, because they are neutralized or absorbed before reaching the place where their action is desired. In this case the insoluble alkaline earths or their carbonates are given. (Strontium and barium are excluded on account of their specific toxicity.) If neutralization without catharsis is required, calcium salts in the form of limewater, chalk, or calcium phosphate would be employed. If the cathartic action is also desirable, magnesium, as the oxid or carbonate, may be used. Catharsis may also be obtained by the addition of vegetable cathartics, such as rhubarb or senna.

(**b**) **Urine.**—The *diuretic action* of alkalies is one which is very frequently employed. As has been pointed out, this is best secured by acetates, to avoid the local action of free alkalies on the alimentary canal. The *increased alkalinity* of the urine is useful in *inflammatory conditions* of the urinary passages, in which the acid urine acts as an irritant. The increased alkalinity has also caused the use of alkalies in gravel, on the theory that they dissolve the uric-acid calculi.

This use is based on the fact that, in the test-tube, free alkalies and their carbonates dissolve uric acid quite readily; so also do certain organic bases like piperazin = diethylendiamin :

$$\begin{array}{l} N = H_2 \\ \vert \\ N = (C_2H_4)_2 \end{array}$$

The conditions are, however, quite different in the body. Alkalies are not excreted as such, nor as carbonates. They cannot, therefore, convert free uric acid into soluble alkaline urates, but at most into acid urates which are almost as insoluble as uric acid itself. It would, therefore, be absolutely impossible to effect in this way the solution of even very small calculi. At the same time, since the urine is less acid, the precipitation of phosphates will be favored, and this may increase the size of the stone.

In some cases, however, alkali may be useful in reducing the acidity of the urine, and thus preventing further increase in the size of the stone. In several instances it has been observed that it caused the breaking up of large stones into small fragments. This cannot be attributed to a solution of the uric acid. The explanation is that probably the calculi were composed originally of small fragments glued together by mucus, and that the alkalies caused the solution of the latter.

Alkalies will also be useful in these conditions by lessening the irritability of the urinary passages. If alkalies are given at all for this purpose they should be in the form of acetates or citrates of potassium or lithium, since these metals form more soluble urates than does sodium.

Urotropin has quite a marked solvent power for urate calculi, when it is excreted by the urine. Since it does not itself possess this property, it must be referred to its decomposition products.

There appears to be still less reason to accept any solvent action of alkalies on uric-acid deposits in the body, although the alkalies, and especially lithium, are still extensively used on this theory in the treatment of gout. Others have attempted to explain their effects by assuming that they cause an increased oxidation of urates into urea. This also cannot be considered as demonstrated. Their employment would, therefore, be entirely empirical. The main reliance in the treatment of gout must still be placed upon proper diet and hygiene.

Their employment in *diabetic coma* has already been discussed (see p. 578). They are also employed against *obesity*, their effects being probably explained, like those of acid, by the derangement of digestion.

(c) **Mucus.**—The solution of mucus by alkali is of use not only in the intestinal canal, but in other situations. It is used in this way as an expectorant. It has also been used in catarrhal dysentery (enemata of 1 : 500 sodium bicarbonate). The false membranes of diphtheria, croup, etc., are also composed largely of mucus, and may be broken down by alkalies. They are best employed in this case in the form of a steam saturated with lime-water, commonly prepared by inhaling the vapors produced by slaking lime in the sick-room.

7. Materia Medica:

ALKALIES.

	CAUSTIC.	AMOUNT FOR BATHS.	STRENGTH OF SOLUTIONS.		INTERNAL DOSE (DILUTED).	
			For Skin.	For Mucous Membranes.	Metric.	Apothecaries.
Soda (U.S.P.), NaOH . .	Sticks.	. . .	2%.	. . .	. . .	. . .
Potassa (U.S.P.), KOH [Potassa Caustica, B.P.]	"	. . .	. . .	. . .	. . .	. . .
Potassa cum Calce (Vienna Paste) (U.S.P.) (eq. parts)	"	. . .	. . .	. . .	. . .	. . .
Calx, CaO (U.S.P., B.P.), and *Calx Hydrata*, B.P., $Ca(OH)_2$	Paste.	. . .	. . .	. . .	. . .	. . .
Magnesia, MgO (U.S.P., B.P.)	. . .	. . .	. . .	. . .	0.3 to 4.0	5 to 60 grs.
Liquor Sodæ, 5% (U.S.P.)	. . .	. . .	. . .	. . .	. . .	. . .
Liquor Sodæ Chloratæ (Labarraque's Sol.) (U.S.P., B.P.)	. . .	. . .	. . .	. . .	. . .	. . .
Liquor Potassæ, 5% (U.S.P., B.P.)	. . .	. . .	. . .	. . .	. . .	. . .
*** *Liquor Calcis* (Saturated) (U.S.P., B.P.) (Lime-water)	. . .	. . .	. . .	. . .	15 to 120 c.c.	1 to 4 oz.
Aqua Ammoniæ Fortior (U.S.P.), 28%	. . .	. . .	. . .	. . .	. . .	. . .
*** *Aqua Ammoniæ* (U.S.P., B.P.), 10%	. . .	. . .	. . .	. . .	1 to 4 c.c.	¼ to 1ʒ
*** *Spiritus Ammoniæ Aromaticus*	. . .	. . .	. . .	. . .	. . .	. . .
Potassii Carbonas (U.S.P., B.P.), K_2CO_3	. . .	100 Gm.	1.5%.	. . .	. . .	. . .
*** *Sodii Carbonas* (U.S.P., B.P.), $Na_2CO_3 + 10H_2O$	. . .	100 Gm.	1.5%.	. . .	0.3 to 1.2	5 to 20 grs.
Lithii Carbonas (U.S.P., B.P.), Li_2CO_3	. . .	. . .	. . .	. . .	0.3 to 1.2	5 to 20 grs.
Ammonii Carbonas (U.S.P., B.P.)	. . .	. . .	. . .	. . .	0.3 to 1.0	5 to 15 grs.
Magnesii Carbonas (U.S.P., B.P.)	. . .	. . .	. . .	. . .	1.0 to 4.0	¼ to 1ʒ
*** *Calcii Carbonas* (U.S.P., B.P.), $CaCO_3$	. . .	. . .	. . .	. . .	1.0 to 4.0	¼ to 1ʒ
*** *Sodii Bicarbonas* (U.S.P., B.P.), $NaHCO_3$ . . .	. . .	100 Gm.	2%.	0.2%.	0.6 to 4.0	10 to 60 grs.
Potassii Bicarbonas (U.S.P., B.P.), $KHCO_3$ . .	. . .	. . .	. . .	. . .	0.6 to 4.0	10 to 60 grs.
*** *Sodii Boras* (U.S.P., B.P.)	. . .	100 Gm.	2%.	0.2%.	0.3 to 2.0	5 to 30 grs.
Sodii Acetas (U.S.P.) .	. . .	. . .	. . .	. . .	0.6 to 2.5	10 to 40 grs.
*** *Potassii Acetas* (U.S.P., B.P.)	. . .	. . .	. . .	. . .	0.6 to 2.5	10 to 40 grs.
Lithii Citras (U.S.P., B.P.)	. . .	. . .	. . .	. . .	0.3 to 1.0	5 to 15 grs.
Lithii Citras Effervescens (U.S.P., B.P.)	. . .	. . .	. . .	. . .	Teaspoonful.	
Potassi Citras (U.S.P., B.P.)	. . .	. . .	. . .	. . .	1.0 to 4.0	15 to 60 grs.
Potassii Citras Effervescens (U.S.P.)	. . .	. . .	. . .	. . .	Teaspoonful.	
*** *Liquor Ammonii Acetatis* (U.S.P., B.P.)	. . .	. . .	. . .	. . .	8 to 30 c.c.	¼ to 1 oz.
Liquor Potassii Citratis (U.S.P.)	. . .	. . .	. . .	. . .	4 to 30 c.c.	1 to 8ʒ
**Piperazin* (Soluble in Water), ...	. . .	. . .	. . .	. . .	0.5 to 1.0	7 to 15 grs.

* Not official.

The most important preparations are marked ***.

⁎*⁎ *Sapo* (U.S.P., B.P.), *Soap* (White Castile Soap, Venice Soap).—An oleate of sodium, prepared from olive oil and soda:

$$\underset{\text{Olive Oil.}}{C_3H_5(C_{18}H_{33}O_2)_3} + 3NaOH = \underset{\text{Soap.}}{3Na(C_{18}H_{33}O_2)} + \underset{\text{Glycerin.}}{C_3H_5(OH)_3}$$

This enters into *Emplastrum Saponis* and *Linimentum Saponis*.

By taking KOH instead of NaOH, soft soap (*Sapo Mollis* (U.S.P., B.P.)—Green soap) results. *Sapo Animalis* (B.P.) is a soda soap made with animal fat.

Soaps are soluble in hot water, but more readily in alcohol.

(D) CARBONIC ACID IN SOLUTION (CARBONATED DRINKS).

These have primarily an acid action, but occupy a somewhat peculiar position. In the first place, CO_2 penetrates very readily on account of its volatility. Unlike other acids, the activity of carbonic acid is not destroyed by neutralization. When absorbed it is fixed in the form of sodium bicarbonate, which is dissociated so readily that it acts both as acid and alkali. For this reason the action of carbonic acid is at once extensive and mild. Taken by the mouth it increases the absorption of food and especially of liquids. In this way it is of very great benefit in fevers. It has also a somewhat specific effect in diminishing vomiting. On account of the stimulation of the sensory nerves of the mucous membranes with which it comes into contact, it is a general reflex stimulant.

(E) MINERAL WATERS.

These will be discussed more in detail in other places, according to their ingredients, but the whole subject may be very briefly summarized in the following compilation:

The action of natural mineral waters has been known empirically since remote times. Their use came about probably by accidental observation and also through the marked taste which they possess.

Springs and Artificial Mineral Waters.—A very striking observation was early made, namely, that these mineral waters, when used at their source, appear to be more effectual than artificial compounds of practically the same composition, or even than the same water when used at a distance.

The most diverse explanations for this have been advanced. Especially in the case of thermal waters, so-called tellurial forces, some mysterious property

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The most important preparations are marked ⁎*⁎.

imparted to them by the earth, have been invoked. Others, again, have laid great stress upon the presence of minimal traces of rare elements, somewhat upon the homeopathic principle. There is nothing in any of these theories. Mineral waters are simply solutions of the ingredients of the soil, and possess only the action of those ingredients which are present in notable amount.

The difference between the water of natural sources and the artificial solutions rests upon other causes, which are sufficiently easy to appreciate, but difficult to reproduce.

These factors refer largely to hygiene and climate. A large proportion of the effects must be attributed to the rest, the freedom from care and business pursuits, the exhilarating effect of improved hygienic, atmospheric, and scenic conditions, better regulation of all the habits, of diet, exercise, etc. The mere drinking of large quantities of fluid is also something which it is difficult to enforce at home, but which the patient does regularly in watering-places. Added to these comes finally the specific action of the dissolved salts.

The effect of mineral *baths* is purely local and reflex. There is ***no absorption*** of the dissolved salts through the skin. The effects are in general the same as with hydrotherapeutics, excepting that they are somewhat stronger.

Mineral waters are either hot or cold. The former are rather stronger and are more readily absorbed (therefore preferred for alkalies); the latter—cold—produce a stronger motor action (hence preferred for cathartics). The salts are contained in mineral waters in *nearly isotonic proportions* and are therefore well adapted for the purpose.

Classification.—These waters are usually classified according to the contained salts. Various classifications are current. The following will be used here:

1. Plain Saline (NaCl).
2. Carbonated:
   - (*a*) Plain.
   - (*b*) Alkaline ($NaHCO_3$).
   - (*c*) Saline (Na_2SO_4).
3. Magnesia.
4. Sulphur.
5. Chalybeate.

Occasional constituents of small importance are Ca, I, Br, Li, and As.

The physiologic effects of the majority of these constituents will be discussed under their respective headings, and will only be very briefly alluded to in this place. It will also be impossible to take up the composition and special indications of the different mineral waters, in anything like an exhaustive manner. It will be necessary to illustrate these classes on only a few well-known waters. It need scarcely be mentioned that the above classification is not an absolutely sharp one, but that many mineral waters belong partly to several classes.

1. Plain Saline Waters.—These are used mainly externally for baths. The most typical is sea-water.

The composition of this is somewhat different in different oceans. In the English channel it is as follows:

1000 parts by weight contain:

NaCl	27.0
KCl	0.75
$MgCl_2$	3.7
MgBr	0.027
$MgSO_4$	2.3
$CaSO_4$	1.4
$CaCO_3$	0.03
Iodids, etc.	traces.

Artificial sea-baths may be made by dissolving 4% of sea- or rock salt in water.

Some of the important saline sources are the following:

European:

	Per 1000: Fixed Salts.	NaCl.	Temperature (C.).
Kissingen[1]	15	11	18.5°
Baden-Baden	28	21	18.5°
Nauheim	30	25	33.0°

American: Saratoga Congress, New York, approaches Kissingen.

2. Carbonated Waters.—(a) Plain.—In these the CO_2 is the main constituent. This aids digestion, and these waters are used mainly as plain table waters. The most used is the artificial soda-water.

An example of a natural carbonated water is Apollinaris:

Per 1000 Gm.:

$NaHCO_3$.	NaCl.	Na_2SO_4.	CO_2.	Temp.
1.2	0.4	0.3	1.5	21°

(b) Alkaline.—These contain a notable amount of $NaHCO_3$. They have the alkaline effects and are therefore useful in gastric catarrh, hyperacidity, hypersecretion of mucus, and as diuretics, in obesity, gout, urate stones, and

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[1] *Formula for Artificial Kissingen* (N.F.):

Potassium Chlorid	17
Sodium Chlorid	337
Magnesium Sulphate	59
Sodium Bicarbonate	107

Twenty-four grains of this to 6 ounces of water (half a teaspoonful to a tumbler is the usual dose).

diabetes. They are most useful when taken hot and drunk very slowly, since in this way they cause the least irritation in the stomach.

(c) **Alkaline Saline Waters.**—These waters contain in addition much Na_2SO_4. The indications for use are the same as for the preceding. The cold waters contain more CO_2 (Marienbad and Franzenbad). The hot alkaline waters are very numerous. The following may be taken as examples:

European Carbonated Alkaline Waters, per 1000:

	$NaHCO_3$.	Free CO_2.	NaCl	Na_2SO_4.	TEMP.
Vichy[1]	5.0	500	. .	. .	40°
Ems	2.0	500	1.0	. .	40°
Selters	1.2	1200	2.3	. .	cold.

Spa, Pyrmont, and Wiesbaden.

American: Saratoga Selters, Saratoga Vichy, Sweet Springs of Virginia, Gettysburg, etc.

(d) Of the *Carbonated saline waters* the most representative is the *Carlsbad*. The formula for the artificial salt is:

K_2SO_4	0.12
Na_2SO_4	2.64
$NaHCO_3$	2.16
NaCl	1.08
	6.00 Gm.

This quantity (a teaspoonful) is the proper amount for a liter (quart) of water.

3. **Magnesia Waters.**—These contain $MgSO_4$, Na_2SO_4, $CaSO_4$, $MgCl_2$, but no CO_2. They are useful as cathartics. If they contain $CaCO_3$, the alkaline action extends deeper into the intestine than in the case of $NaHCO_3$.

European, in 1000 Gm.:

	$MgSO_4$.	Na_2SO_4.	$CaSO_4$.	NaCl.	$MgCl_2$.
Hunyadi János	22.3	22.5	. .	1.3	. .
Seidlitz	13.5	. .	1.4	. .	0.4

Epsom and Friedrichshall belong to the same class.

American: Crab Orchard, Kentucky, and Bedford Springs, Pennsylvania.

4. **Sulphur Waters.**—These contain free H_2S and sulphids. Externally they stimulate the skin and soften the epidermis; internally they act as cathartics. They have quite a reputation in the treatment of chronic rheumatism. Some

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[1] *Formula for Artificial Vichy* (N.F.):

Sodium Bicarbonate	846.0 Gm.
Potassium Carbonate	38.5 "
Magnesium Sulphate	38.5 "
Sodium Chlorid	77.0 "

Fourteen grains to 6 ounces of water (¼ teaspoonful to a tumbler is the dose).

examples are: Aix-la-Chapelle, Harrogate, Virginia Sulphur Springs. The following will give an idea of their composition:

In 1000 Gm.:

	Free H_2S.	Na_2SO_4.	NaCl.	TEMP.
Aix-les-Bains	0.003	0.092	0.030	44°

5. **Chalybeate Waters.**—These contain Fe, usually as bicarbonate, also NaCl and Na_2SO_4. The amount of iron is from 0.01 to 0.12 of FeO per liter. The most famous springs are: Tunbridge and Brighton in England; Pyrmont, Wiesbaden, and Spa on the Continent; Bedford, Pittsburg, Brandywine, and several Virginia springs, in the United States.

(F) CLIMATE.

This is of such great importance in the action of mineral waters that it may be discussed in this place. Only the roughest sketch can be given, and the student must refer to larger text-books for further description.

The principal elements which enter into the climate are the following:

1. Air:
    - Moisture.
    - Temperature.
    - Purity.[1]
    - Density (Altitude).
    - Special Constituents.[2]
2. Sunlight.
3. Water, Purity of.
4. Conditions of Life—comfort, hygiene, rest, diversion, pleasant surroundings, out-of-door life, etc.

The subject of climatology is very largely empirical. The work which has been done on the effect of the different climates upon metabolism, nutrition, etc., is as yet too limited to be of great value.

The *principal climates used in therapeutics* are:

1. Sea.
2. Dry and Warm.
3. Elevated.

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[1] Purity: This refers especially to the absence of bacteria, but other fixed impurities may also be of importance; *e. g.*, the causation of hay-fever by pollen. In cities, various chemic gases may also be deleterious impurities.

[2] Of such special constituents, the aromatic oils given off by needle-trees may be of considerable value as antiseptics in phthisis. The presence of ozone, if it is of any importance, serves mainly to indicate the general purity of the atmosphere.

1. Sea Climate (Including Islands and Sea Voyage).—The important effects of this are related to constant temperature, humidity, and purity of the atmosphere, and to general surrounding conditions.

This climate, being very restful, is especially useful in cases of overwork. The freedom from atmospheric impurities also renders it valuable in hay-fever and phthisis.

2. Dry and warm climate, such as in deserts and Egypt, southwestern Texas, inland Southern California, or in the pine sections of Georgia and the Carolinas.

The special advantage of this climate consists in its permitting outdoor life in winter. It is peculiarly valuable in lung disorders which do not stand a northern temperature.

3. Elevated Climates.—These are generally aseptic, and the air is cool and dry. What importance can be given to the rarefaction of the atmosphere is not at present clear, still less the manner in which this acts.

The rate of the heart and respiration is at first increased, but later it returns to normal.

These climates cause improvement in a number of conditions, probably in part due to a greater exercise of the organs from climbing, etc. They are *useful* in dyspepsia, anemia, chlorosis, insomnia, asthma, and consumption.

High climates are *unfavorable* to feeble conditions of the heart and vessels, which cases should be sent to the seashore.

CHAPTER XXVII.

SYSTEMIC (ION) ACTION OF METALLIC SALTS.[1]

I. ABSORPTION, ETC.

Absorbable and Non-absorbable Metals.—In the cases of metals one must distinguish between the local and remote actions. Every metallic salt has a local action; in addition, every metallic salt which is dissociable into ions has a toxic action if it is introduced into the circulation. It does not matter whether the metal is arsenic or iron; even the degree of the toxicity is practically the same in both cases if they are actually introduced into the body. (The alimentary canal is not, in this sense, "within the body.") The main difference between the two metals consists in the fact that arsenic is easily absorbed, while iron, like most other metals, is not. Arsenic, mercury, and uranium are the only metals the absorption of which is of an extent sufficient to cause acute poisoning with non-corrosive doses. Phosphorus, which behaves pharmacologically in many respects like metals, is absorbed still more readily. Certain other metals are absorbed much more slowly. To this class belong lead, silver, tin, and iron. Any metallic salt, if given in strong solution, will cause *corrosion* of the mucous membrane of the alimentary canal and will then be absorbed, and would exert its toxic action were it not that the local effects kill before the systemic can come into play.

A peculiarity of the corrosion produced in this manner is that there seems to be a possibility of acquiring a certain immunity to it. If the administration of a metallic salt is begun with small doses and gradually increased, it becomes possible to administer without effect doses which would at first have produced violent corrosion.

To be absorbed, the metal must of course be in soluble form; but it must be borne in mind that the solubility in the alimentary canal is not necessarily the same as the solubility in water in a test-tube. In fact, it makes little difference, except as regards local action, in what form a metal is administered. In the stomach it will be converted largely into the chlorid; in the intestines into the carbonate and sulphid. Further, the metallic salts enter into double combinations with proteids, and these are often soluble in an excess of the latter. In this way such insoluble compounds as mercuric oxid, mercurous chlorid, lead sulphate, and silver chlorid, may be brought into solution.

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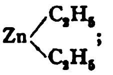
[1] The materia medica of all metallic salts (including those used only locally) will be given in this chapter. The nature and therapeutic uses of the local actions are discussed in Chapter XXVIII.

Absorption is one factor necessary to produce the toxic action. A second factor is that the compound must contain the metal in a *dissociable form*—*i. e.*, in the form of ions. This is not the case with the pure metals nor with some organic compounds, such as



$$Zn\begin{cases} C_2H_5 \\ C_2H_5 \end{cases};$$

nor with the iron of ferro- and ferricyanids. In these combinations the metals form a firmer part of the molecules. However, both the pure metals and the organic compounds are in most cases split up in the body into dissociable compounds, and so finally come to exert the metal action, but only after dissociation.

II. REMOTE ACTION.

To obtain the systemic action of most metals these must be injected directly into the blood or at least subcutaneously, on account of the limited absorption. But it would not do to inject the ordinary metallic salts, for these precipitate the blood proteids and cause the formation of emboli, which would obscure the results. Soluble combinations which will not precipitate must be chosen: Such can be formed by combining the metallic salts with proteids previous to administration, or by taking double salts (like the double citrate of iron and ammonium).

When such a preparation is injected directly into the blood the symptoms in many cases do not arise at once, but are *developed quite slowly*, sometimes only in the course of several days. This is due to the fact that the metals do not act in the blood, but only after they have been absorbed into the cells; and this absorption is so slow that it may take several days to accumulate sufficient metal to produce any action. It may by this time have disappeared entirely from the circulating liquids.

The *excretion* of the metals is usually even slower than their absorption. They have therefore often a cumulative action; doses too small to produce any immediate effect will cause serious poisoning if long continued. Pb, Hg, and As are the most prominent examples of this. In whatever manner the metal is introduced into the circulation—whether intravenously, hypodermically, or from the intestinal canal—it is excreted partly by the kidneys, but the main part leaves through the intestines, especially the large. The epithelial cells are the channel of this excretion, and not to any extent the bile, as was at one time supposed. A *gastro-enteritis* may result from local action even when the poison has been given intravenously. On this account tartar emetic, for instance, acts largely locally even when administered intravenously or hypodermically.

A sufficient amount of the metals, however, is excreted by the kidneys to cause a marked nephritis, characterized in the ordinary manner by albuminuria, casts, etc. The *nephritis* begins in the epithelium of the convoluted tubules and spreads from here to the glomeruli. If the poisoning is chronic, the nephritis may become interstitial and lead to renal cirrhosis.

In their *systemic effects*, all the metals show a striking similarity. They affect mainly the circulation. There is a very marked *fall of blood pressure*, which is due partly to a *paralysis of the blood-vessels* and partly to a *direct action on the heart*. Secondary to this disturbed circulation there arise symptoms from the *central nervous system*. A direct effect upon nervous organs is not common in mammals, and is only conspicuous with silver. Frogs show with most metals a paralysis, preceded by a slight stimulation. The tetanizing action predominates with Ni, Co, and Pt. Whether the metals have any direct effect on *metabolism* cannot be decided with our present methods, because of the disturbances introduced by the intestinal and renal irritation, and by the circulatory changes.

The metals, aside from silver, may be divided into *two principal groups*: the first group acting mainly peripherally on the *blood-vessels*, the second group acting peripherally on the *heart*. To the first group belong arsenic, antimony, uranium, bismuth, iron, manganese, selenium, tellurium, aluminium, tin, nickel, cobalt, gold, and platinum; to the second group, lead, phosphorus, copper, zinc, cadmium, mercury, vanadium, cerium, and thallium,

III. ARSENIC.

The general actions of metals can be best illustrated on Arsenic. We stated that only those combinations of metals are toxic which are decomposable into ions. In the case of arsenic, even those which do not contain the arsenic as ion are decomposed in the body into salts from which the arsenic ion is liberated; so that all preparations are toxic. However, arsenious acid and the arsenites are most strongly so.

I. SUMMARY OF ACTIONS.

A *relaxation of the walls of the capillaries*, particularly of the splanchnic area, accompanied by an increased permeability, and consequently by changes similar to those of inflammation. As this is shown mainly in the splanchnic area, the most conspicuous symptoms are those of a *gastro-enteritis*, which resemble closely those of cholera.

This dilatation of capillaries introduces changes in the circulation which cause secondary disturbances in the function of more remote organs, particularly in the *nervous system;* and further, fatty degeneration of the cells, particularly in glands and muscles, with other disturbances in metabolism. There may also be a direct paralysis of the *heart*, both ganglionic and muscular.

II. DETAILS OF ACTION.

The action of arsenic may be either acute or chronic. Very little essential difference has been made out between the two, beyond some direct corrosion in the former. Both rest upon the paralysis of the capillaries.

1. **Acute arsenic-poisoning** sets in very rapidly, pointing to a quick absorption. The first *symptoms* are an acute *gastro-enteritis*, and resemble so closely those which result from corrosive poisoning that they were formerly believed to be due to this. However, the autopsy rarely shows extensive corrosion, and it is known that the corrosive action occurs extremely slowly.[1] Furthermore, the gastro-enteritis may be obtained with at least equal readiness if the arsenic is injected into the circulation or subcutaneously. This

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[1] The principal use which is now made of this corrosive action is in killing the nerves of teeth. This takes several days, which illustrates the slowness of the corrosive action, and contrasts very strikingly with the extremely rapid onset of the symptoms in acute poisoning.

would not definitely exclude all local action, since some arsenic is excreted into the alimentary canal; but the quantity is not nearly enough to account for the symptoms.

Simultaneously with the violent vomiting and purging of the gastro-enteritis there is an extremely marked *fall of blood pressure*. This is *almost entirely vascular in origin;* for if the aorta is clamped, the heart is able to maintain a fairly high presssure. This vascular paralysis is *mainly peripheral*, but it differs from that produced by the nitrites, for stimulation of the peripheral stump of the splanchnic nerve is still. effective in raising the blood pressure, at least in the earlier stages. The arterioles must therefore still be capable of contracting. For this reason it is assumed that structures beyond the arterioles—namely, *the capillaries—are the seat of the paralysis*. This view is favored by the fact that they have become more permeable. (Intravenous injections of large quantities of salt solution will cause edema in animals poisoned with As, but not in the normal.) There is in addition a weakening of the heart, and probably also some depression of the vasomotor center and partial paralysis of the arterioles. All these contribute to the fall of pressure.

These changes in the capillaries explain practically the whole course of the poisoning. Since *increased permeability* of the capillaries is one of the essential features of inflammation, one need not be surprised that the phenomena of arsenic-poisoning are similar to those produced by an irritating inflammation, although the primal cause is different.

The first and strongest effects are upon the *intestine*, no matter how the arsenic has been introduced. The capillary paralysis results in the production of an exudation into the connective tissue. This raises the epithelium (just as would a blister on the skin), and causes it to be thrown off in shreds or false membranes. The exudation is then poured into the lumen of the intestine and largely coagulates. This distention, as well as the circulatory changes, causes increased peristalsis and *watery diarrhea;* and the shreds of mucus and coagulated exudation give to the evacuations the character of "*rice-water*" *stools*.

The pathology of this condition is exactly the same as that of Asiatic cholera, and without a history it is absolutely impossible to distinguish between the two conditions except by chemic examination of the dejections.

The extreme distention of the capillaries may lead to their rupture, to the formation of ecchymoses, or possibly bleeding into the intestine or stomach, and consequently bloody vomiting or diarrhea; but this is by no means always the case.

The great distention of the splanchnic area will of course withdraw a great amount of blood from the general circulation, and this will react upon other organs. In some cases this effect is so violent that it produces collapse, from paralysis of the central nervous system, before the symptoms of enteritis have had time to develop. This corresponds exactly to "dry cholera."

Besides this indirect action on various organs, due to the altered distribution of the blood, arsenic also has some *direct actions*, particularly upon the *heart*. It paralyzes its rhythmic power after the manner of hydrocyanic acid, and also depresses its contractility. But its other direct actions are entirely overshadowed by that on the capillaries and the indirect consequences of this.

Death usually occurs by exhaustion as a result of the prolonged gastro-enteritis, as in cholera. There are the same muscle cramps, paleness, and general collapse. The patient appears emaciated from the withdrawal of liquid from the body by the profuse diarrhea, and this even if he retains a fair amount of adipose tissue.

2. Chronic Arsenic-poisoning.—With a still less acute action a *chronic gastro-intestinal catarrh* is developed, possibly with ulceration. The less intense but persistent capillary paralysis will give time for the development of more pronounced *degenerative changes* in other parts of the body. Most prominent amongst these are fatty degenerations, first of the *endothelium* of the capillaries themselves. Later this affects the *intestinal epithelium*, and finally the cells of other organs—*liver*, *kidney*, *heart muscle*, etc. This is due to the interference with nutrition. The increased size of the liver from the fatty degeneration may cause pressure on the bile ducts, consequently reabsorption of bile and icterus. In the chronic action of arsenic there is quite a tendency to the development of *local effusions*. Amongst the first of these is *swelling of the eyelids*, which is fairly characteristic.

The impaired nutrition of the nerve-trunks gives rise to *polyneuritis*, with atrophy of the muscles, disturbance and paralysis of sensation, and also of the special senses. The *voice* is very frequently altered, from paralysis of the vocal cords. The *skin* is also particularly subject to the action of arsenic, perhaps because it takes part in its excretion. This action results in acne-like eruptions, exfoliation, and in falling out of hair and detachment of finger-nails. In a few cases a peculiar cutaneous *melanosis* can be noticed. This is not due to a deposition of arsenic, but to the formation of an organic pigment. The mucous membranes, especially the conjunctivæ, may also suffer.

3. **Beneficial Action on Metabolism.**—If the doses of arsenic are extremely small, this capillary dilatation and hyperemia may not reach a harmful degree, and may even lead to an increased nutrition. This deserves especial attention, since it is the rational basis of the use of arsenic in the various cachectic conditions. This metabolic action is quite variable, as it depends upon a number of mutually opposed causes. Amongst these are: the capillary dilatation; supposedly a direct action of arsenic upon the cells; and the action upon the gastro-intestinal canal and upon the kidneys. The interaction of these factors may produce very different results. Consequently the experimental data are not of very much value. It may be considered as proven, however, that as long as the arsenic does not interfere with digestion and absorption, it *increases* the *excretion of nitrogen*. If this interference is avoided, arsenic also causes *increased deposition of fat*. Another effect which is found in arsenic-poisoning is the loss of the glycogen of the liver and formation of sarcolactic acid.[1] What practical importance can be attributed to this is not at present clear. The diminution of glycogen is so rapid that it cannot be ascribed to a diminished power of forming it. Nor does it seem to be connected with the lactic acid formation.

One of the therapeutic uses of arsenic is to *increase the number of erythrocytes*. There seems to be considerable evidence that it does so in certain forms of anemia, by stimulating the bone-marrow. It has no such effect in normal animals. Arsenic also leads to *thickening of the bones* and filling up of the Haversian canals, which may possibly justify its use in rickets.

On the whole, there can be no doubt that in some cases the early use of arsenic *increases the rate of growth and weight* of the animal; in detail, causing an increase in nitrogen metabolism and a deposition of fat and an increased strength of the bones. The nutrition of the *skin* is also said to be especially improved by it. It is used quite largely in veterinary practice to give the coats of horses and cattle a bright appearance. Its use to improve the complexion is not rare. The people of certain countries—the mountainous districts of Silesia—use it to secure an *improvement in general health.* There appears to be unimpeachable evidence that they gradually accustom themselves to use quantities which would be fatal to ordinary individuals. This *acquired immunity* is the more strange since it has never been attained with animals. The fact that the corrosive action of other metals can to a large extent be lost by habituation is perhaps suggestive, but it is impossible to say whether the two phenomena are connected.

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[1] Other poisons which cause diminution of glycogen are: Phosphorus, mercuric chlorid, chloroform, colchicin, and nitrobenzol.

III. ABSORPTION AND EXCRETION.

Arsenic is very readily **absorbed,** even from the unbroken skin. Quite a number of cases of poisoning have occurred in this way from the use of arsenical cosmetic preparations. When it is injected subcutaneously the diarrhea often sets in within an hour.

It is **excreted** by all the excretions,—urine, feces, sweat, milk, and epithelium of the skin,—but so slowly that it may be discovered in the urine five months after the last dose has been taken.[1] It is stored in all organs; not especially in the liver, as was at one time claimed. It also passes across the placental circulation to the fetus. It is just as toxic when injected into the mesenteric, as by the jugular vein, showing that the liver neither neutralizes nor retains it. It is less toxic on hypodermic injection, since it enters into more slowly dissociated compounds with the tissue elements.

Chronic arsenic-poisoning may result from a single dose insufficient to produce death; or it may result from repeated small doses, in which case it will be slow to develop. This points to the fact that the arsenic is not excreted as fast as it is absorbed—that it accumulates in the body. And this, indeed, has been proved by direct experiment.

A very small amount of arsenic is normally present in certain human organs, notably in the thyroid (0.16 mg.); also in the thymus, brain, and skin. It appears to be tied to the nuclein. None is found in the liver.

Arsenic is toxic to all animals which possess a central nervous system; also to most of the higher plants, but not to all the lower organisms. Its antiseptic action is comparatively small. It cannot therefore be classed as a general protoplasmic poison.

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[1] The time required for the excretion varies with the animals: It is given as 160 days for dogs, 120 days for rabbits, and 70 days for man.

IV. TOXICOLOGY.

The main interest of arsenic lies in its toxicology.

1. **Etiology.**—Arsenic was at one time used very extensively for criminal poisoning, especially in the seventeenth century. An Italian woman, Toffania, carried this science to its greatest refinement, using under the name of "Acqua Toffana" a mixture of arsenic and ptomains obtained from the putrefied saliva of animals poisoned with arsenic.

At the present time arsenic is rarely used with criminal intent, the most frequent forms of poisoning being suicidal or accidental. This may be attributed to the perfection of the chemic means of detection, which allow of the discovery of the minutest trace.[1] Accidental poisoning has been lessened to some extent by requiring the preparations of arsenic sold at retail to be colored either with lamp-black or indigo, so that they do not have the innocent appearance of a white powder. This is also of some importance in diagnosing the poisoning, the color of the vomit calling attention to it. But accidental poisoning is yet very common, since arsenic is so extensively distributed. It is easy to obtain it as rat and fly poison. It is frequently used in the arts. Paris green is a preparation whose sale is almost unrestricted. A great many of the cosmetic preparations on the market contain arsenic and have given rise to accidents. The use of arsenic compounds, such as Schweinfurth green, as pigments has been absolutely prohibited; but a great many of the coal-tar dyes, which are popular at the present time, employ arsenic in their preparation, and very frequently this is not entirely removed. Formerly wall-paper dyed with arsenic compounds was a common source of arsenic poisoning, but this has now practically disappeared.

The **fatal dose** of arsenic is upward of a decigram.

The **course** of arsenic-poisoning may be very quick. There is a fulminant type in which death is almost immediate. The usual course, however, takes from eighteen to seventy-two hours. In some cases it may take much longer—from four to fourteen days.

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[1] A very delicate biologic test has recently been announced, depending upon the development of a garlic-like odor, when the mold Penicillium brevicaule is grown upon an arsenical medium. Quantities as small as $\frac{1}{100}$ to $\frac{1}{500}$ mg. of arsenious acid could be demonstrated by its aid.

2. The **symptoms** have been sufficiently discussed, but will bear recapitulation. In **acute poisoning** there may be a sudden collapse without other symptoms. Usually, however, the symptoms do not appear for from one-half to one hour after the arsenic is taken. The suspicion of the patient may have been aroused by the sweetish astringent taste of the substance. Almost the first symptoms are vomiting and profuse and painful diarrhea. The withdrawal of water from the body leads to great thirst, dryness of the mouth and throat, and difficulty in swallowing and articulation. The urine is diminished and often bloody. The excretion of the arsenic through the kidneys will produce a nephritis. On the part of the central nervous system there are vertigo, headache, and pain in the limbs. There will be cyanosis and cold extremities. Toward the end occur syncope, coma, clonic and tonic spasms, and a general paralysis.

In the **subacute poisoning** the inflammation of the mucous membrane of the alimentary canal will form a still more prominent symptom. Inflammation of other mucous membranes also becomes conspicuous, and shows as conjunctivitis, coryza, stomatitis, salivation, and pharyngitis. Skin eruptions make their appearance if the arsenic-poisoning is at all prolonged. In this case there are also symptoms arising from the central nervous system, as well as neurites.

The **diagnosis of acute arsenic-poisoning** is made by the violent gastro-enteritis. This can usually be distinguished quite easily from that produced by acids and alkalies, by the history of the case, absence of corrosion in the mouth, and furthermore by the lesser prominence of the local symptoms. The very quick onset distinguishes it from other metals.

The **diagnosis of chronic arsenic-poisoning** may be somewhat difficult because the symptoms are sometimes quite obscure or resemble very closely those produced by chronic lead-poisoning. There is some difference in the electric reaction of muscle and the absence of the blue line on the gums, which are characteristic of lead. But in other cases of the acute or chronic form the chemic examination is the only absolute means of making the diagnosis.

3. In the **postmortem examination** there would be a very pronounced dryness of the tissues. The emaciated appearance of the body, even with a fair amount of adipose tissue, the appearance of the alimentary canal with its large amount of fluid and the presence of shreds of mucus and false membrane, with usually no pronounced corrosion, are characteristic. Microscopically gastro-adenitis and cell infiltration are often seen. The body after arsenic-poisoning usually putrefies very slowly and may become mummified, which always causes a suspicion, although it is not at all a proof of such poisoning.

4. The best **treatment of arsenic-poisoning** is the rendering insoluble of the arsenic by ferric hydrate—best made by adding some calcined magnesia to a solution of ferric csulphate. (See *Ferri Oxidum Hydratum cum Magnesia*). A very large amount of this can be given. The compound formed in this manner is comparatively insoluble, but not entirely so, and it should be removed by lavage of the stomach. The magnesia in this mixture also acts usefully as a purgative, removing the arsenic from the intestine.

V. THERAPEUTICS.

As to the therapeutics of arsenic, it has some *local uses* which will be discussed among the caustics. Its **systemic action** is used for the improvement of nutrition in various cachectic conditions. Although it is easily understood how it may be of benefit in these cases, its actual use must be entirely empirical. We do not know sufficient about the nature of these conditions, nor can we predict the action of arsenic with sufficient certainty, to be able to foretell its results. It is usually worthy of a trial in such cachectic conditions as malaria, pernicous anemia, etc. In chlorosis it seems to aid the iron preparations, but does not act alone. Its use in rickets has been alluded to (p. 605). It has been used in chorea (rapidly increasing doses), phthisis, and asthma, but clinicians disagree as to its value, and there is no scientific basis for its employment.

In its **administration**, it should be aimed to establish immunity by beginning with small doses, and gradually increasing these until some local manifestation of the arsenic appears—usually diarrhea or conjunctivitis or swelling of the eyelids. As soon as these are seen, the amount must be diminished.

VI. MATERIA MEDICA OF ARSENIC.

Solid Preparations:

⁂ *Acidum Arsenosum* (U.S.P.) [*Acidum Arseniosum*, B.P.].—*Arsenious Acid, White Arsenic.* As_2O_3. Solubility in water, 30 or 80 parts. *Dose:* 0.001 to 0.006 Gm. ($\frac{1}{60}$ to $\frac{1}{10}$ grain).

Sodii Arsenas (U.S.P.).—Na_2HAsO_4. Solubility in water, 4 parts. *Dose:* 0.001 to 0.006 Gm. ($\frac{1}{60}$ to $\frac{1}{10}$ grain).

Arsenii Iodidum (U.S.P., B.P.).—AsI_3. Solubility in water, 7 parts. *Dose:* 0.001 to 0.006 Gm. ($\frac{1}{60}$ to $\frac{1}{10}$ grain).

* *Ferri Arsenas.*—Insoluble. *Dose:* 0.001 to 0.006 Gm. ($\frac{1}{60}$ to $\frac{1}{10}$ grain).

Liquid Preparations.—All contain 1% of the arsenic preparation and have the *dose* of 0.12 to 0.6 c.c. (2 to 10 minims).

Liq. Acidi Arsenosi (U.S.P.) [*Liq. Arsenii Hydrochlorici*, B.P.].—Contains 0.5% HCl.

⁂ *Liq. Potassii Arsenitis* (U.S.P.) [*Liq. Arsenicalis*, B.P.].—(*Fowler's Solution.*)—Flavored with Sp. Lavand. Co.

Liq. Sodii Arsenatis (U.S.P., B.P.).

Liq. Arseni et Hydrargyri Iodidi (U.S.P., B.P.).—(*Donovan's Solution.*) Contains 1% of each.

VII. SELENIUM AND TELLURIUM.

Selenium and Tellurium resemble arsenic in the general action on the capillaries of the splanchnic area. They also affect the central nervous system, apparently directly. Tellurates arrest perspiration (after the manner of atropin?), and have been recommended for this purpose; but they impart a very persistent garlic odor to the breath, tissues, urine, and feces, even in a quantity as small as 0.005 mg.! This may last for several months after the administration is stopped. It is caused by methyl-tellurid.

* *Sodii Telluras.*—Na_2TeO_4.—*Dose:* 0.016 to 0.05 Gm. ($\frac{1}{4}$ to $\frac{3}{4}$ grain).

IV. ANTIMONY.

1. The **actions** of antimony bear a close resemblance to those of arsenic. The difference lies in a greater local irritation and a much less absorption. Consequently, *when given by the mouth*, doses can be chosen whose only action is that of producing nausea, or if somewhat larger, vomiting. If *injected into the circulation*, or if given in overdoses, it produces precisely the same effects as arsenic, but vomiting is always a prominent phenomenon, the poison being rapidly excreted into the alimentary canal. Small doses long continued lead to a train of symptoms of *subacute poisoning*, entirely analogous to those produced by arsenic in the same manner.

The **treatment** is the same as for arsenic, except that tannin (tea, etc.), or in its absence magnesia, is used as an antidote.

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* Not official.

The most important preparations are marked ⁂.

Applied to the skin, the chlorid is a strong caustic. The double tartrate of antimony and potash (tartar emetic) produces a pustular eruption. This is due to the decomposition of the double salt, which is but slightly irritant, by the acid secretion of the follicles into more irritant simple salts.

2. **Therapeutically** the tartar emetic is the salt most frequently employed *internally*. As an *emetic* it has fallen out of favor, its action being too slow and too depressing. As a *nauseant* it has advantages over all other metals, since the dose required for this is only about one-tenth of that which produces vomiting. The sulphid is preferred by some, since this dissolves much more slowly, and therefore has a more lasting action. Antimony preparations are useful as diaphoretics and expectorants (see p. 303 and 529).

For *local uses* see Chapter XXVIII.

MATERIA MEDICA OF ANTIMONY.

Solid Preparations:

Antimonii Sulphidum Purificatum (U.S.P.) [*Antimonium Nigrum Purificatum*, B.P.].—*Sulphid* (Trisulphid) *of Antimony* (*Black Antimony*).—Sb_2S_3. The native sulphid, purified by washing with ammonia water. Insoluble black powder. Used only in the preparation of the other compounds.

Antimonium Sulphuratum (U.S.P., B.P.).—(*Kermes Mineral.*) Consists chiefly of Sb_2S_3 with a small amount of Sb_2O_3. Made by dissolving Sb_2S_3 in NaOH and precipitating with H_2SO_4. Insoluble reddish powder. *Dose:* 0.01 to 0.06 Gm. (1/6 to 1 grain).

This is contained in:

Pilulæ Antimonii Compositæ (U.S.P.) (*Plummer's Pill*):

Each pill contains:

	GRAMS.	GRAINS.
Sulphurated Antimony	0.04	2/3
Calomel	0.04	2/3
Guaiac	0.08	1 1/3

Dose: 1 to 3.

Antimonii Oxidum (U.S.P., B.P.).— Sb_2O_3. A gray powder obtained by precipitating antimony chlorid with water, and treating with Na_2CO_3. *Dose:* 0.06 to 0.24 Gm. (1 to 4 grains).

⁂ *Antimonii et Potassii Tartras* (U.S.P.) [*Antimonium Tartaratum*, B.P.].—*Tartar Emetic* (*Tartarus Stibiatus*).—$2K(SbO)C_4H_4O_6 + H_2O$. White crystals or powder, prepared by treating Sb_2O_3 with acid potassium tartrate. Soluble in 17 parts water, insoluble in alcohol. *Dose:* 0.006 to 0.03 Gm. (1/10 to 1/2 grain) for Expectorant and Diaphoretic; 0.06 to 0.12 Gm. (1 to 2 grains) for Emetic.

Liquid Preparations:

⁂ *Vinum Antimonii* (U.S.P.) [*Vinum Antimoniale*, B.P.].—0.4% Tartar Emetic (℥j = gr. ij). *Dose:* Expectorant, 0.3 to 4 c.c. (5 to 60 minims); Emetic, 4 to 15 c.c. (ʒj to iv).

The most important preparations are marked ⁂.

⁎*⁎ *Syrupus Scillæ Compositus* (U.S.P.) (*Hive Syrup*):

Contains:	In 100 c.c.:	In ʒj:
Squills	8.0 Gm.	4 grains.
Senega	8.0 "	4 "
Tartar Emetic	0.2 "	1/10 grain.

Used especially in whooping-cough. *Dose:* 0.3 to 2 c.c. (5 to 30 minims).

V. URANIUM.

This is one of the most poisonous of metals. The uranium salts are very corrosive, and are in consequence readily absorbed from the alimentary canal. Their action resembles that of arsenic, but in addition they lessen internal respiration after the manner of hydrocyanic acid.

The symptoms of poisoning include a severe gastro-enteritis, with ecchymoses. Degeneration of the walls of blood-vessels and of organs occurs. There is a strong nephritis; the amount and specific gravity of the urine are increased, and it contains sugar and albumin. The glycosuria is probably an expression of the "internal asphyxia."

The metal has *no therapeutic indications.*

* *Uranium Nitrate.*—Soluble. *Dose:* 0.01 to 0.02 Gm. (1/6 to 1/3 grain).

VI. BISMUTH.

The therapeutic importance of this metal lies in the local action of its basic salts. These are brought into solution by the acidity of the gastric juice (and act in this way as antacids). It is not easily absorbed from the alimentary canal even when dissolved, but general poisoning has occurred through the absorption of the basic salts from open wound surfaces.

If it is injected directly into the blood, it produces the arsenic phenomena on blood-vessels. There is perhaps also a direct involvement of the central nervous system and depression of the vasomotor center. The heart-muscle is also depressed. The blood pressure sinks, therefore, very rapidly.

Bismuth forms a black and very insoluble sulphid. Since H_2S is always present in the large intestine, this is always colored black. When the bismuth is in the blood, the precipitation may occur in the vessels of the large intestine, and lead to capillary embolism, and this to ulceration. Therapeutically, the avidity for H_2S serves to remove this irritant from the intestinal canal, and the benefits of bismuth may be due to this, in certain cases.

MATERIA MEDICA.

1. **Insoluble Salts.**—*Dose:* 0.3 to 4 Gm. (5 to 60 grains). (White powders, tasteless and odorless.)

Bismuthi Subcarbonas (U.S.P., B.P.).—$(BiO)_2CO_3 + x\,H_2O$. Prepared by pouring a solution of $Bi(NO_3)_3$ into Na_2CO_3.

⁎*⁎ *Bismuthi Subnitras* (U.S.P, B.P.).—$BiONO_3 + x\,H_2O$. Prepared by pouring a solution of $Bi(NO_3)_3$ into water.

Bismuthi Citras (U.S.P.).—Treating bismuth subnitrate with citric acid.

Bismuthi Salicylas (B.P.).

* *Bismuth Subgallate* (*Dermatol*).—Dry yellow powder, recommended especially as absorbent antiseptic.

Many other insoluble organic bismuth salts and proteid compounds are also found on the market, but in view of the non-corrosive character of the ordinary subnitrate, it is difficult to see in what they are superior.

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* Not official.

The most important preparations are marked ⁎*⁎.

2. **Soluble Bismuth Salts and Their Preparations.**—The value of bismuth preparations lies precisely in their sparing solubility, so that the following are not scientific:

Bismuthi et Ammonii Citras (U.S.P.).—Bismuth Citrate dissolved in Ammonia and dried to scales. Very soluble in water, sparingly in alcohol. *Dose:* 0.12 to 0.3 Gm. (2 to 5 grains).

* *Elixir Bismuthi* (N.F.).—3.5% Citrate of Bismuth and Ammonia.

Liquor Bismuthi et Ammonii Citratis (B.P.).—*Dose:* 2 to 4 c.c. (½ to 1 drachm).

VII. IRON.

When *injected directly into the circulation* this metal produces effects which resemble those of arsenic very closely. (Preparations which do not precipitate proteids must be used.) Hypodermic injections may give the same result. Large amounts of concentrated iron salts also produce corrosion when introduced into the stomach, and may then give rise to analogous symptoms. When given in moderate concentration there is no marked absorption, and it produces almost no immediate action.

Late and remote actions of iron have been very carefully and persistently sought for, to support the time-honored use of iron in anemias. This use dates from the remotest time; even the ancients, who knew nothing about the importance of iron in the blood, left swords to rust in water, and then drank this water as a remedy for the same diseases against which iron is now employed. When the presence of iron in hemoglobin was discovered, it seemed to furnish a rational basis for the use of iron salts. However, the more the action has been studied, the less tenable does such a simple explanation become. At one time the beneficial effects of iron were denied altogether. This extreme has also been recovered from. At the present day, it is conceded by practically all therapeutists that neither iron nor any other drug can raise the hemoglobin when its amount is normal; but when it is abnormally low, iron, no matter in what form it is given, will increase the hemoglobin. How it does this is still in dispute.

Iron also occurs in the liver, spleen, bone-marrow, kidneys, and other organs, where it can be demonstrated by microchemic reactions. Indeed, it probably forms a necessary component of every cell. (Its importance to plants has also been established, although it does not occur in the chlorophyl, as was at one time believed.) A diminution of the iron stock of the body may, therefore, be expected to act directly upon all the cells—a fact which is so overshadowed by the much more conspicuous diminution of hemoglobin that it has not received the attention which it deserves.

Theories of the Action of Iron.—The view that iron is simply absorbed as such and converted into hemoglobin having become untenable, a large number of theories have been advanced to explain its action. A great many of these are now only of historic interest. At the present time *two distinct theories* are in the field.

According to the first theory, the improvement after the iron is due to the absorption and gradual utilization of iron, whether it is given in organic or inorganic form.[1]

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[1] By "*organic iron*" preparations in this connection is meant the form in which iron exists in the cells and in the food; namely, not as an ion, but in

* Not official.

The second theory is that iron can be absorbed if it is given in the organic form, but that inorganic iron is not assimilated, and acts by improving the processes of digestion and absorption, or in some other manner, without itself entering into the formation of the hemoglobin.

Up to quite a recent date it was altogether a moot question whether iron was absorbed at all in any form other than that in which it naturally exists in food. This having been settled in the affirmative in the case of certain organic iron preparations, it was still questioned in the case of the inorganic iron. This also is now answered in the affirmative, the only point in dispute being whether the absorbed inorganic iron can be utilized or whether it simply plays the rôle of the carbon particles in the lungs, which are also "absorbed," carried in the lymph, and deposited in certain organs, but which take no part in metabolism, as does "organic" carbon, say in the form of sugar or fat.

(A) It might, at first view, seem a very easy problem to determine by **chemic methods** whether iron is absorbed or not. But one cannot determine it, as in the case of nitrogen, by estimating the *difference between the iron in the food and in the feces*, since the intestine is the channel of excretion, as well as of absorption, of iron. Indeed, iron is not excreted by the urine, except in small amounts. Even when it is given hypodermically it can be shown that while the injected iron has largely disappeared from the body, only a small part has gone into the urine. The main amount has been *excreted by the intestine*—not so much by the bile as was at one time supposed, but by the epithelial cells, especially of the large intestine. The gastric juice contains only very faint traces. It is, therefore, impossible to say whether the iron existing in the feces is unabsorbed or excreted. In experiments extending over but few days, the iron in the feces is very frequently greater than that in the food. In extending such observations

firm combination with the organic constituents. In this form it lacks the chemic character of iron salts; it does not immediately give precipitation, for instance, with ammonium sulphid; it cannot be separated by electrolysis, and cannot be split off by acidified alcohol. The inorganic iron preparations are those which give the reactions mentioned. It does not matter whether the Fe is combined with an inorganic acid, as in sulphate of iron, or with organic acids, as in the acetate or even albuminate. (Iron, like all metals, gives a precipitate with proteids, but it exists in this combination as "inorganic iron." It can be easily split off from this, and differs in every respect from the so-called organic iron found in the food and in the body.)

over long periods it is shown that the iron income and outgo are very nearly evenly balanced. But this also does not show whether the iron in the body is renewed during this time by absorption and excretion : One would be entitled to believe that no iron was absorbed, and that the body simply utilized its own stock over and over again. This, however, is disproved by the fact that the feces of starving individuals contain iron ; so that it must be excreted, and, consequently, absorbed. Absorption is also proved by the fact that the adult contains more iron than a young animal. All this serves to show that the method of income and outgo is not adapted to solving the question, for it does not even prove with certainty any absorption under conditions in which there is a rapid gain. It only suffices to show that the quantity of iron which may be absorbed from any preparation whatsoever cannot be greater than a few milligrams. This evidence is very unsatisfactory ; for these few milligrams, were they absorbed, would be of the greatest importance, since we know by other methods that the normal absorption is no more than 10 milligrams per day, and probably much less.

Very long-continued accurate observations would, of course, give tangible results, but these are almost impracticable. It was, therefore, attempted to trace the iron into the body. Since iron is already found there, and the small difference which would result from its absorption could not be recognized with certainty, it was attempted to solve the difficulty by the administration of a metal very closely allied to iron—viz., *manganese*—on the assumption that it would suffer the same fate as iron. The result of these experiments showed that Mn is not at all absorbed except when given in corrosive doses. It was argued from this that the inorganic iron preparations are also incapable of absorption. The weak point in this argument lies, of course, in the assumption that the absorption of iron is the same as that of manganese. When one considers the chemic similarity of As and Sb and the difference in their absorption, the reasoning from analogy becomes at once untenable. Indeed, as we shall have occasion to see, inorganic iron is actually absorbed.

Still another method employed to study the question by chemic means was to estimate the *total quantity of iron in the body* of an animal fed for a considerable time on the preparations to be investigated, as compared with that in a control animal.

A new-born animal contains a larger percentage of iron in its tissues than an adult. This is a useful provision, because milk, upon which the animal feeds during the first days of its life, contains a proportion of iron which would be entirely insufficient for its nutrition. Consequently during the first days of life—in the guinea-pig and rabbit something like the first seventeen days—the iron stock percentage diminishes. This continues up to the time when the animal begins to take solid food containing a larger percentage of iron than does milk. At this time all the animals of a litter contain practically the same amount of iron in their bodies. If they are now put on different dietaries, or upon the same diet with or without the iron preparations to be investigated, the amount absorbed can be calculated by comparing the amount of iron in their bodies with that found in the control animals.

By this method positive results have been obtained by all observers for food-iron and for certain forms of organic iron; but the results for inorganic iron are not uniform for different experimenters.

The reason for this must be sought in the difficulty of excluding absorption by corrosive action. Unskilful administration might lead to large absorption, while more careful experimenters would find little or no absorption under similar conditions. It seems probable that with careful experiments the quantity absorbed from inorganic iron preparations is too small to be demonstrated with certainty by this method. But, even were it demonstrated, this would not exclude the idea that the increase was due, not to absorption of the inorganic iron itself, but to its increasing the absorption of food-iron according to the theories to be mentioned later.

The chemic methods have, therefore, not accomplished much for the solution of the question. The conclusions to which they have led may be *summarized* as follows (Bunge):

1. It has not been proved (by chemic methods) that inorganic iron, given in small amounts (1 or 2 decigrams per day for man), is absorbed. The possibility of a slight absorption must be granted.

2. If larger quantities of iron are given, or if the administration of small amounts is continued for a long time, a part of the iron is absorbed. It has not been shown that the iron absorbed in this manner is assimilated. The possibility of such assimilation must be granted.

3. It is certain that iron given in the organic form, or as contained in food, is largely absorbed (and assimilated).

(B) For all our modern knowledge concerning the absorption and assimilation of iron we are indebted to **microchemic methods.**

Iron exists in the body in a number of *different forms:*

1. Dissolved, as in hemoglobin. In this form it does not

give any iron reaction with ferrocyanid even after the action of acids; nor with $(NH_4)_2S$.

2. In granules. These give a more or less pronounced iron reaction after the action of acids. These granules are found in the liver, spleen, bone-marrow, and other organs. They appear more abundant in certain situations when iron preparations are administered. In this way they furnish a guide to the absorption and fate of iron preparations, as follows:

Absorption of Iron.—Iron, whether inorganic, organic, or food-iron, is absorbed only from a limited part of the small intestine. The absorption begins at the pylorus and extends a very small distance downward, the distance being proportional to the amount of iron given, and varying also according to the preparation used.

Inorganic iron is converted into an albuminate, as a preliminary to its absorption. This is again decomposed by the pancreas and bile, and so becomes again incapable of absorption. In this way the conditions for absorption are only favorable for a short distance. This is perhaps one reason for the greater absorption of organic irons. These are not converted into albuminates, and are not so readily decomposed by the pancreatic juice, so that their absorption extends further down the intestine.

The absorption must presumably take place through the epithelium, but the iron passes through so rapidly that it cannot be made out in the cells. It is next seen lying as granules in the leucocytes of the mucosa. With inorganic iron preparations the leucocytes collect in abnormal numbers toward the tips of the villi. These leucocytes, mostly of the eosinophile variety, carry the iron partly to the mesenteric glands, partly into the portal vein. The radicles of the latter also take up iron in a dissolved condition, so that their endothelium and serum give the iron reaction after treatment with acids.

The greater part seems to be carried to the liver and deposited in the liver-cells, at first toward the periphery, later toward the center of the lobules. Here the granules derived from the inorganic iron behave very differently from those originating from the food and organic iron; the latter resemble in all respects the granules normally found in the liver and other organs; the former are very much more easily split up by acids, and retain this property, so that they are probably never converted into body iron.

A certain amount of deposition also takes place in the spleen and bone-marrow. The granules of organic iron are stored in these organs and are supposed to be converted, as needed, through some intermediate form into hemoglobin and other dissolved iron ; but here the microchemic methods fail us, and nothing definite is known until *excretion* is reached. The granules again make their appearance at the places of excretion—*i. e.*, the cells of Lieberkühn's crypts in the cecum of the large intestine and rectum. Granules are also seen in the kidneys, and part of the iron is excreted in the bile. The relative quantities leaving by these channels appear to be variable. The conditions which influence them are not known.

In pregnancy the iron which goes to the fetus comes largely from the spleen. This can be seen by histologic methods. The average iron-content of the spleen is also shown to be lowered by chemic analysis.

(C) Effect of Iron on Hemoglobin Formation.—All the facts so far presented show only that the iron is absorbed and deposited in the liver and other organs. It does not yet form a part of the protoplasmic molecule. Until it does so, it may practically be considered "outside of the body." No matter how much iron may be presented to the organism, no matter how much or in what form it is absorbed, it is not converted into protoplasmic iron at once, but is stored in the intermediate granule-form, until required. On this account it is *impossible to increase the hemoglobin beyond the normal limit*, although it is possible to increase the iron in the body. The only way in which such iron can be normally of any conceivable benefit is in young animals, which it may enable to grow more rapidly. In normal adults, with the normal amount of iron in the food and the normal excretion and absorption, an increase of the iron in the food and its increased absorption would, therefore, have no effect whatsoever upon the hemoglobin.

How is it in conditions in which the hemoglobin is *subnormal?* Can this artificial administration of iron be utilized in this condition, and does it lead to an increase of hemoglobin? It is mainly in the answer to this question that the authorities disagree.

It may be stated at once that *iron in any form is capable of increasing the hemoglobin in anemia.* But this is not equivalent to saying that it acts by being converted into hemoglobin. To justify such a statement it would be necessary to prove, first, that the amount of iron presented in the food for absorption is not sufficient for the needs of the organism ; and, second, that the absorbed artificial iron is fit to replace this deficiency.

In regard to the latter, it has been determined that the organic iron suffices to supply the iron needed for the additional hemoglobin of the growing organism. Inorganic iron increases the hemoglobin, both in growing animals and after hemorrhage, if the organic iron of the food is abundant; more than would be the case if the same diet were given without the inorganic iron. But when it is given with an iron-free diet, it does not increase the hemoglobin.

Some observers have claimed the opposite. It is not unlikely that in these cases there was a large amount of iron stored in the body.

In other words, while it appears that organic iron may be converted into hemoglobin, it seems that inorganic iron is incapable of this change, but increases the power of the organism to utilize the organic iron.

It has also been demonstrated directly that the administration of these inorganic iron preparations causes an increased activity in the formation of red corpuscles in bone-marrow, especially after hemorrhage.

The appearance of the intestine after the ingestion of inorganic iron salts is suggestive of the explanation of this stimulation. It has been mentioned that leucocytes occur in unusual numbers at the tips of the villi where the iron absorption occurs. It is not unlikely that the presence of the iron granules deposited in the spleen and bone-marrow also stimulates the action of the corpuscle-forming cells in these organs, in an analogous manner.

Application of Iron to the Treatment of Anemias:

The above is the gist of the rather voluminous literature on the experimental side of the action of iron. It now remains to apply this, to explain the acknowledged clinical data, and to endeavor to formulate the rules which should guide its administration.

1. Iron has been extensively used in the treatment of **chlorosis** and other forms of anemia. Although success is not uniform, it is so frequent as to leave no doubt about its value in many cases. As to whether the inorganic or the organic form is the most efficient, and as to the relative value of small or large doses, the statements of clinicians are so discordant that it is difficult to avoid the suspicion that their judgment has to some extent been influenced by their preconceived views concerning the action of iron and the nature of chlorosis.

To arrive at any satisfactory conclusions, it will be necessary to have a clear conception of the nature of the diseases. In chlorosis the most striking symptom is the deficiency of hemoglobin in the blood, the corpuscles not being decreased in a corresponding degree. The iron in the blood is proportionately diminished.[1]

This is, however, not the only symptom. Lessened appetite and constipation are also usually very conspicuous. It is easy to see how each of these two conditions—*i. e.*, digestive disturbances and want of hemoglobin—would tend to aid in the production of the other. Stockman has shown that whereas the normal diet contains 6 to 14 mg. of iron (not 59 to 109, as was formerly claimed), that of chlorotic girls contains only 2.8 to 3.2 mg., an amount which must certainly be considered inadequate. However, no one has ever been able to produce chlorosis by limitation of the iron in the food. The fact that it is peculiar to females at the age of puberty suffices to show that the *essential* condition is not want of iron in the diet. Nor will it be found that the patients improve as rapidly as might be expected when the difference is made good by the addition of even a fairly large excess of organic assimilable iron to the food. The primary cause must not, therefore, be sought in a deficient introduction of iron, but in its *faulty absorption or assimilation.* It is not unlikely that both are involved, and the aim should be to make the conditions for both as favorable as possible. But it may be unhesitatingly granted that the diminished supply of iron must be a contributory factor to the condition, and the first indication would seem to be to *reestablish the normal iron-content in the food.* This may

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[1] Jolles and Winkler give the following figures for the iron in the blood and urine in certain diseases:

	IRON IN 1 LITER OF BLOOD.	IRON IN DAY'S URINE.
Normal	540 to 720 mg.	4.6 to 10.0 mg.
Catarrhal icterus .	222 "	
Grave anemia . .	197 to 254 "	28.0 to 52.0 "
Chlorosis	260 to 299 "	6.8 to 7.7 "
Leucemia	274 "	8.7 "
Malaria	300 "	18.7 "

be done either by well-selected dietaries [1] or by stimulating the appetite by bitters, exercise, inhalation of oxygen, etc. But since the amount of the absorbing surface is proportional to the amount of iron (see p. 617), it would be indicated to administer much more than the normal amount of iron. This could not be done by food, but would necessitate the employment of *organic iron preparations.*

Following the first meritorious work in this direction, innumerable such preparations have been introduced into the market. There appears to be no reason for believing that one preparation is superior to another, and the cheapest should be preferred. This would be hemoglobin. The gastric juice converts this into hematin, which is absorbed like other organic irons. Since blood is rather disgusting to many patients, it would be well to employ the precipitated and dried hematin, which can be given in pill form.

This would be the extent of the usefulness of organic iron, but inorganic iron would also aid in the absorption and assimilation of the organic iron.

Since the absorbing surface is limited by the precipitation of the iron by the intestinal juices, the organic and food iron may be *protected by inorganic iron,* which is more readily

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[1] The following *table of iron-content* is abridged from Bunge:

	MILLIGRAMS OF Fe IN 100 GM. DRY SUBSTANCE.
Egg-white	trace.
Rice	1.0–2.0
* Wheat flour, fine	1.6
Barley	4.5
Rye	4.9
* Whole wheat	5.5 *
Potatoes	6.4
Peas	6.2–6.6
Carrots	8.6
* Wheat bran	8.8
Apples	13
Green leaves of cabbage	17
Meat (beef)	17
Asparagus	20
Yolk of egg	10–24
Spinach	33–39
Blood (pigs)	226
Hematogen	290
Hemoglobin	340

To these may be added from Stockman:

	MgFe.
In 1000 c.c. milk	3.8
In 100 Gm. oatmeal (= 88 dried)	3.14
In 100 Gm. white bread (= 70 dried)	0.6
In 100 Gm. lean beefsteak (= 27 dried)	3.9

* The iron of wheat is near the outer portion of the grain, and coarse bread, containing as much as possible of the bran, should be preferred for chlorotic patients.

precipitated, and would, therefore, extend the absorbing surface.

This precipitation is mainly dependent on the alkalinity of the pancreatic juice and bile, not on the presence of abnormal quantities of H_2S, as was at one time supposed. But if the latter is present, it will also be neutralized by the inorganic iron. In either case, iron salts could be replaced by the salts of other metals; indeed, manganese has given fairly good results.

Iron is also an *astringent* and mild irritant, and may in this way conceivably so alter the state of a diseased mucous membrane as to increase its absorbing power.

This may be the case in theory, but it can scarcely be said to rest on proof. The quantity of iron would have to be just right. Larger quantities would cause corrosion, and may make the administration of any form of iron impossible.

Much more positive evidence has already been cited to show that the small quantities of inorganic iron which are absorbed stimulate the foci of blood formation. We are inclined to attribute to this the greater part of its effects. It will be remembered that arsenic acts in a similar manner, and may to some extent replace iron, although it is not nearly so efficient.

From the above it will be seen that inorganic iron preparations may be expected to strike more deeply at the root of the disorder than organic; but the latter may be expected to effect a more rapid, though less permanent, improvement. It would seem, then, that both forms are indicated at once. We have already expressed our preference for crude hematin among the organic iron preparations. As to inorganic preparations, it must be remembered that the amount absorbed, as well as the protection to organic iron, will be proportional to the amount given; again, that the soluble acid salts are more efficient than the insoluble carbonate, or especially still more than the reduced iron, since these have to be converted into soluble salts before they can act. It must also be remembered that excessive doses lead to deleterious irritation or to constipation. The dose should be so adjusted by experience in each individual case as to avoid these. The constipation may be relieved by laxatives. It is further to be borne in mind that the iron preparations should not be very corrosive. This is the objection to the chlorid, and it seems to us that the sulphate or lactate would be more promising.

To sum up the measures which should enter into the *treatment of chlorosis:*

Hygiene: proper air and exercise.

Diet: plentiful and rich in iron; bitters (gentian) and laxatives (aloes).

Organic and inorganic iron. (Substitutes for inorganic iron: manganese and arsenic.)

2. The pathology of **other anemias** is still more obscure than that of chlorosis. The table in the foot-note on page 620 shows that an increased disassimilation of iron is very prominent, and the microscopic examination often reveals large quantities in the liver, spleen, etc. In hemorrhage, on the other hand, these organs are poor in iron. In many anemias, therefore, the organic iron does not seem to be wanting, but inorganic iron might possibly improve the condition; whilst in anemia from loss of blood the same treatment would be indicated as in the case of chlorosis.

MATERIA MEDICA OF IRON.[1]

(Manner of preparation, see p. 66. Ferric salts have a reddish, ferrous a greenish, color.)

1. **Preparations Used Only Externally:**

Ferri Chloridum (U.S.P.).—$Fe_2Cl_6 + 12H_2O$. Freely soluble in water.

Liquor Ferri Chloridi (U.S.P.) = about 38% of the anhydrous salt, or 13% Fe.

Liquor Ferri Perchloridi Fortis (B.P.) = 22½% Fe.

Liquor Ferri Nitratis (U.S.P.) = about 6% of $Fe_2(NO_3)_6$ = 1.4% Fe.

Liquor Ferri Nitratis (B.P.) = 3.3% Fe.

⁂ *Liquor Ferri Subsulphatis* (U.S.P.) (*Monsel's Solution*, made by oxidizing Fe_2SO_4 with HNO_3 and H_2SO_4) = 13.6% Fe.

Liquor Ferri Tersulphatis (U.S.P., B.P.) = about 29% of $Fe_2(SO_4)_3$ = 8% Fe.

This is used in the preparation of

Ferri Oxidum Hydratum cum Magnesia (U.S.P.) (*Arsenic Antidote*).

The following should be kept on hand:

A: Liquor Ferri Tersulphatis 10, Water 100.
B: Magnesia 10, Water 800.

When wanted, B is well shaken, A is added, and the mixture is shaken until smooth. It is given in tablespoonful doses, very frequently repeated, and followed by lavage or emetic, and a saline purgative.

2. **Insoluble Inorganic Preparations:**

Ferrum Reductum (U.S.P., B.P.).—By reduction of ferric oxid by hydrogen. *Dose:* 0.06 to 0.3 Gm. (1 to 5 grains).

Trochiscus Ferri Reducti (B.P.).—Each contains 1 grain.

Ferri Carbonas Saccharatus (U.S.P., B.P.).—Made by precipitating $FeSO_4$ with $NaHCO_3$. Greenish-brown powder of sweetish ferruginous taste; easily oxidized in air. *Dose:* 0.12 to to 0.6 Gm. (2 to 10 grains).

Ferrous Carbonate is also contained in:

Massa Ferri Carbonatis (U.S.P.).—(*Vallet's Mass.*) Used in pill form. *Dose:* 0.06 to 0.3 Gm. (1 to 5 grains).

⁂ *Pilulæ Ferri Carbonatis* (U.S.P.) [*Pilula Ferri*,. B.P.].—[*Blaud's* (*Chalybeate*) *Pills.*] *Dose:* 1 to 2 (5 to 10 grains, B.P.).

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[1] The official iron preparations are by far too numerous, and many could well be dispensed with.

The most important preparations are marked ⁂.

Ferri Oxidum Hydratum (U.S.P.).—(*Ferric Hydrate.*) $Fe_2(OH)_6$. Made by precipitating Ferric Sulphate with Ammonia. Used in the preparation of other salts.

Pil. Aloes et Ferri (U.S.P., B.P.).—*Dose:* B.P., 0.25 to 0.5 Gm. (4 to 8 grains).

3. Solid Soluble Inorganic Salts:[1]

		SULUBILITY:		DOSE:	
		Water.	Alcohol.	Grams.	Grains.
Ferrous.	*Ferri Sulphas* (U.S.P., B.P.) (Copperas, Green Vitriol), $FeSO_4 + 7H_2O$	1.8	Insol.	0.03 to 0.12	½ to 2
	⁂ *Ferri Sulphas Exsiccatus* (U.S.P., B.P.), $FeSO_4$ (for use in pills)			0.03 to 0.12	½ to 2
	Ferri Iodidum Saccharatum (U.S.P.)	7.0	"	0.3 to 1.0	5 to 15
	Pilulæ Ferri Iodidi (U.S.P.)			one or two	
	⁂ *Ferri Lactas* (U.S.P.), $Fe(C_3H_5O_3) + 3H_2O$	40.0	"	0.06 to 0.3	1 to 5
	Ferri et Ammonii Sulphas (U.S.P.)(*Ferric Alum.*), $Fe_2(NH_4)_2(SO_4)_4 + 24H_2O$	3.0	"	0.12 to 0.6	2 to 10
	† *Ferri Phosphas Solubilis* (U.S.P).	Freely.		0.06 to 0.3	1 to 5
	Ferri Phosphas (B.P.)	Insol.		0.3 to 0.6	5 to 10
	† *Ferri et Potassii Tartras* (U.S.P.) [*Ferrum Tartratum*, B.P.]	Freely.	"	0.3 to 1.0	5 to 15
	⁂ † *Ferri et Ammonii Citras* (U.S.P., B.P.)	"	"	0.06 to 0.3	1 to 5
	† *Ferri et Ammonii Tartras* (U.S.P.)	"	"	0.3 to 1.0	5 to 15
	† *Ferri Citras* (U.S.P.)	Slowly.	"	0.06 to 0.3	1 to 5
	† *Ferri et Quininæ Citras Solubilis* (U.S.P.)	"	"	0.12 to 0.6	2 to 10
	Ferri et Quininæ Citras (U.S.P., B.P.)	Partly.			
	† *Ferri Pyrophosphas Solubilis* (U.S.P.)	Freely.		0.06 to 0.3	1 to 5
	Ferri Hypophosphis (U.S.P.)	Insol.	"	0.3 to 1.0	5 to 15
	* *Ferrum Albuminatum*, 5% Fe_2O_3			1	15
	* *Ferrum Albuminatum Peptonisatum*, 0.25%			1	15
	⁂ *Ferrum Caseinatum*, 52%			1	15

4. Liquid Inorganic Iron Preparations, Simple[2]:

	DOSE:	
Syrupus Ferri Iodidi (U.S.P., B.P), 10% FeI_2	0.3 to 2 c.c.	5 to 30 min.
⁂ *Tinctura Ferri Chloridi* (U.S.P.), 10% of Fe_2Cl_6 (to be largely diluted)	0.3 to 4 c.c.	5 to 60 min.

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[1] Those marked † are scale preparations, made from Ferric Citrate, by adding the appropriate reagent and drying on glass. They have an uncertain composition.

[2] The liquid preparations of iron have a very injurious effect upon the teeth if brought in contact with them. They should therefore be taken through a glass tube, and the mouth rinsed thoroughly.

* Not official.

The most important preparations are marked ⁂.

	Dose:	
Liquor Ferri et Ammonii Acetatis (U.S.P.) (*Basham's Mixture*) . .	4 to 15 c.c.	1 to 4 drachms.
⁂ *Liquor Ferri Citratis* (U.S.P.), 7.5% Fe (to be largely diluted) .	0.3 to 1.0 c.c.	5 to 15 min.
Liquor Ferri Acetatis (U.S.P., B.P.) (to be largely diluted) . .	0.12 to 0.6 c.c.	2 to 10 min.
* *Ferrum Dialysatum*, a 10% aqueous solution of ferric oxychlorid, freed from excess of HCl by dialysis (to be largely diluted)	0.6 to 2.0 c.c.	10 to 30 min.
⁂ *Elixir Ferri Phosphatis* (N.F.), 3.5% Ferric Phosphate	2 to 4 c.c.	30 to 60 min.
Liquor Ferri Perchloridi (B.P.) and *Tinctura Ferri Perchloridi* (B.P.). (Each contains one-fourth of the stronger solution.)	0.3 to 1 c.c.	5 to 15 min.
Syrupus Ferri Phosphatis (B.P.) (1 drachm = 1 grain)	4 to 8 c.c.	1 to 2 drachms.
⁂ *Vinum Ferri Citratis* (U.S.P., B.P.)	4 to 15 c.c.	1 to 4 drachms.
Vinum Ferri (B.P.)	4 to 15 c.c.	1 to 4 drachms.

5. **Liquid Inorganic Iron Preparations, Compound:**[1]

	Dose:	
	C.c.	Drachms.
Mistura Ferri Composita (U.S.P., B.P.) (*Griffith's Mixture*). About 0.7% of Ferrous Carbonate in suspension in flavored water	8 to 15	2 to 4
Syrupus Ferri, Quininæ, et Strychninæ Phosphatum (U.S.P.) (*Easton's Syrup*) [*Syrupus Ferri Phosphatis cum Quinina et Strychnina* (B.P.)]	2 to 4	½ to 1
Ferric Phosphate 2%		
Quinin Phosphate 3%		
Strychnin 0.02%		
* *Elixir Ferri, Quininæ, et Strychninæ Phosphatum* (N.F.)	2 to 4	½ to 1
Ferric Phosphate 1.75%		
Quinin 0.9%		
Strychnin 0.0275%		
⁂ *Vinum Ferri Amarum* (U.S.P.) (Iron and Quinin Citrate, 5%, flavored with orange)	4 to 15	1 to 4
Syrupus Hypophosphitum cum Ferro (U.S.P.) . . .	15 to 30	4 to 8

6. **Iron (Chalybeate) Mineral Waters.**—These contain the iron most often as ferric bicarbonate; sometimes as sulphate, oxid, and very rarely as chlorid.

7. **Organic Iron Preparations.**—Only the standard scientific preparations can be considered in this connection. *None are official.* The *dose* is usually 1 Gm.

(a) Artificial Preparations:

	Percentage of Iron.
Ferratin: Originally prepared from liver, but at present obtained artificially	7.0

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[1] Elixir Gentian Compound is recommended when it is desired to prescribe a simple bitter with iron.

* Not official.

The most important preparations are marked ⁂.

(b) From Blood:

	Percentage of Iron.
Hemoglobin: *Hematin:* Both could be used advantageously as dried blood, with and without previous treatment with acids.	
Hemols: Obtained by the reduction of hemoglobin through zinc dust (or by other metals)	0.2
Hemogallol: Obtained by precipitating blood by pyrogallol	

(c) From Other Sources:

Hematogen (Bunge): A nucleo-proteid from egg yolk	0.3

Various other nucleo-proteids are also used, such as *Ferratogen*, obtained by the artificial digestion of yeast grown on media containing iron; = 1 % Fe.

VIII. MANGANESE AND CHROMIUM.

Manganese and chromium are not absorbed in sufficient amount to have any general action, the phenomena in poisoning by the soluble salts (permanganates, chromates, etc.) being entirely local; *i. e.*, exerted upon intestines and kidneys. This holds true even when the soluble preparations are introduced into the circulation.

Manganese dioxid is sometimes used empirically as an emmenagogue, or to replace iron in its other uses, but is of very questionable utility.

MATERIA MEDICA.

	Solubility in Water.	Dose: Metric.	Apothecaries'.
Mangani Dioxidum (U.S.P.), MnO_2	Insol.	0.12 to 0.6	2 to 10 grains.
Mangani Sulphas (U.S.P.), $MnSO_4 + 4H_2O$	0.8	0.12 to 0.6	2 to 10 grains.
Potassii Permanganas (U.S. P., B.P.), $KMnO_4$ . . .	16	0.03 to 0.12	½ to 2 grains.
**Syrupus Ferri et Mangani Iodidi* (N.F.)		4 to 8	1 to 2 drachms.
Acidum Chromicum (U.S.P., B.P.), CrO_3	Very sol.	Only externally.	
Potassii Bichromas (U.S.P., B.P.), K_2CrO_7	200	0.01 to 0.03	⅙ to ½ grain.
Liquor Acidi Chromici (B.P.), 25 %		Only externally.	

IX. ALUMINIUM.

The salts of this metal have a purely local action when given by the mouth; they are not at all absorbed from the intact alimentary canal. Even very large doses cause only a local exudative inflammation (hence vomiting and diarrhea). This is due to their precipitating proteids. They are therefore antiseptic and astringent. The precipitate is, however, soluble in an excess of proteid. They spread very slowly even when injected subcutaneously, and appear to penetrate cells with the greatest difficulty; for the symptoms appear only several days after the injection, at a time when the metal has entirely disappeared from the blood, and has become fixed in the cells. The symptoms then resemble those of subacute arsenic-poisoning. They never occur when aluminium salts are given by mouth, no matter in what doses, nor how long continued. Much stress is laid by manufacturers of baking powders upon the injurious effects of alum. It is evident that these must be purely local on the alimentary canal. It can scarcely be doubted that the continued administration of even small doses has deleterious effects. The quantities which may be dissolved from aluminium cooking vessels, even by dilute acids, are too small to be of any importance.

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* Not official.

MATERIA MEDICA.

	SOLUBILITY IN WATER.	DOSE: Metric.	DOSE: Apothecaries'.
⁂ *Alumen* (U.S.P., B.P.), *Alum.* $Al_2K_2(SO_4)_2 + 24\,H_2O$. (For external use see gargles, injections, eye-waters, etc., 2%; for tonsillitis, 20% glycerite as paint) . .	9	0.03 to 2.0	5 to 30 grains.
Alumen Exsiccatum (U.S.P.), *Burnt Alum.* (Alum from which the water of crystallization has been expelled by roasting.) Used locally in powder form as styptic .	20		
Alumini Hydras (U.S.P.), $Al_2(OH)_6$. By precipitating alum with Na_2CO_3	Insol.	0.06 to 0.6	1 to 10 grains.
Alumini Sulphas (U.S.P.), $Al_2(SO_4)_3$	1.2		
Alumnol (Beta-naphthol-disulfonate of aluminium). Antiseptic astringent; 1% to 5% aq. solution, or as dusting-powder (mixed with 5 to 10 parts starch or talcum) . .			
Glycerinum Aluminis (B.P.), 10% .			

X. COBALT AND NICKEL.

These metals are only absorbed when given in strongest solutions or when long continued. The local action is that of metals in general, with nothing particularly characteristic. Nickel salts have been used as emetics, but are not to be recommended.

When introduced into the circulation they affect the central nervous system directly, in addition to the usual metal action on capillaries, heart, and kidneys. There are tremors, chorea, and convulsions, followed by paresis. In frogs the medulla is stimulated before the spinal cord.

The urine is increased, and always contains sugar, often proteids. Cobalt salts act as antidotes to HCN poisoning, through the formation of cobalt-cyanids. To be effective they must be introduced subcutaneously in doses which are not devoid of danger. It is therefore not to be used in man.

The most important preparations are marked ⁂.

MATERIA MEDICA.

* *Niccoli Bromidum.*—Freely soluble. *Dose:* 0.13 to 0.52 Gm. (2 to 8 grains).

XI. SILVER.

This metal is absorbed in extremely small amount, and is reduced to the inactive metallic state as soon as it enters the body. For this reason it can never lead to general poisoning, and the only evidence of its absorption lies in a dark discoloration (argyrism) of the skin and certain situations, after its prolonged administration. This is due to the deposition of metallic silver in the connective tissue of the corium, the sweat glands, in smooth muscle, villi of intestine, etc. It is not seen in most animals.

If the silver is introduced into the circulation its effects differ from those of other metals in the predominance of nervous symptoms. These are central and mainly paralytic. There is motor paralysis beginning in the hind legs, depression of the respiratory center with asphyxial convulsions, stimulation of the vasoconstrictor center, followed by paralysis, etc. The secretion of bronchial mucus is so greatly increased that it may lead to asphyxia. This is probably due to injury to the epithelium.

The *therapeutic employment* of silver in insanity, etc., is a survival of the fantastic teaching of the middle ages, when it was based on its dedication to the moon, and the supposed connection of the latter with lunacy. Although it is absolutely proved that silver cannot be absorbed in amounts sufficient to have any action whatsoever, it has been tried again and again against all forms of nervous disease, with uniformly negative results. The indications for it are purely local.

MATERIA MEDICA.

	SOLUBILITY IN WATER.	DOSE:	
		Metric.	Apothecaries'.
⁂ *Argenti Nitras* (U.S.P., B.P.), *Silver Nitrate* (Lunar Caustic), $AgNO_3$	0.6	0.015 to 0.06	¼ to 1 grain.
If given internally, it is best made into pills with clay and vaselin.			
Externally in ⅕% to 2% solution. (See eye-waters, injections, ulcers, etc.)			

* Not official.

The most important preparations are marked ⁂.

	Solubility in Water.	Dose:	
		Metric.	Apothecaries'.
Argenti Nitras Induratus (B.P.). Contains 5% of KNO_3 and fused into rods			
Argenti Nitras Dilutus (U.S.P.) [*Arg. Nitr. Mitigatus*, B.P.] (*Mitigated Caustic*). Made by fusing 3 parts $AgNO_3$ and 6 parts KNO_3.			
⁂ *Argenti Nitras Fusus* (U.S.P.) (Lunar Caustic in sticks). Contains a small quantity of chlorid.			
Argenti Oxidum, Ag_2O (U.S.P., B.P.)	Insol.	0.03 to 0.12	½ to 2 grains.
Argenti Iodidum, AgI (U.S.P.) . .	Insol.	0.015 to 0.06	¼ to 1 grain.
A large number of patented organic silver preparations have appeared on the market. Their object is to diminish the caustic effect whilst retaining the astringent and antiseptic action.			
Argonin. A casein compound containing 4% Ag. Used as urethral injection in solutions of 1 to 7 : 1000. Said to be one-twentieth as irritant as the nitrate	Soluble with heat.		

XII. GOLD AND PLATINUM.

Gold and platinum are still more easily reduced to the metallic state than is silver, and are therefore devoid of general action when taken by the mouth. When injected into the circulation they produce an arsenic action. They should have no place in rational therapeutics.

MATERIA MEDICA.

Auri et Sodii Chloridum (U.S.P.).—*Dose:* 0.002 to 0.006 Gm. (1/30 to 1/10 grain).

* *Liq. Auri et Arsenii Bromidi* (N.F.).—*Dose:* 0.06 to 0.5 c.c. (1 to 8 minims).

Gold Tribromid	0.325%
Arsenic Tribromid	0.65%

XIII. TIN.

This metal is absorbed in part even from non-corrosive preparations. But poisoning is very rare, the metal not passing very easily into soluble form, and having no pronounced tendency to cumulative action. The symptoms on injection devolve to some extent on the central nervous system, as stimulation and subsequent paralysis. The arsenic action and paresis of heart are also prominent. With more chronic poisoning the gastro-enteritis is most marked, but there is also an ataxia and motor paralysis, resembling chronic lead-poisoning.

XIV. VANADIUM AND CERIUM.

These have the usual metal action, the cardiac symptoms predominating.

Vanadium, in the form of vanadate of lithium, has recently been recommended in diabetes, it being claimed that it reduces the sugar to one-half. It has also been used as an alterative, similar to arsenic, which it closely resembles in its actions.

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* Not official.

The most important preparations are marked ⁂.

Cerium oxalate and nitrate are used as antiemetics.

Neither has any pharmacologic basis, and the clinical results are not very decisive.

MATERIA MEDICA.

Cerii Oxalas (U.S.P).—Insoluble white powder. *Dose:* 0.06 to 0.5 Gm. (1 to 8 grains).

* *Lithii Vanadas.—Dose:* 0.004 to 0.005 Gm. per day (1/10 grain).

XV. COPPER, ZINC, AND CADMIUM.

These metals are closely related in their action. Given by the mouth, copper and zinc salts have a rather specific irritant action, affecting at first exclusively the nerve structures which form the starting-point of the *vomiting* reflex. In consequence, vomiting occurs before there is time for corrosion, and even very large doses present no danger. Nor is there any danger of chronic poisoning. This is of some impcrtance on account of the use of copper to give a green color to preserved *vegetables.* These contain 0.20 to 0.50 mg. of Cu per kilogram. It is, of course, conceivable that copper salts may become deleterious through their continued local action, but the quantities introduced with these vegetables may be affirmed to have no such effects.

The local irritation by Cu and Zn causes these to be used as emetics (see p. 329). The nausea is too short to allow of their use as expectorants.

If *introduced into the circulation* they cause death through paralysis of the cardiac muscle. They also affect the central nervous system, probably directly, especially Zinc and Cadmium. The effects are mainly paralytic. The brain is affected first,—*i. e.*, consciousness is lost,—but the motor areas are not involved. The blood pressure falls rapidly, but this is mainly due to the cardiac depression.

Copper depresses the excised skeletal muscles, whilst Cadmium (and probably Zinc) has little action upon them.

Zinc Oxid has been used *therapeutically* against epilepsy. Its usefulness is doubtful, but not disproved.

MATERIA MEDICA.

⁂ *Cupri Sulphas* (U.S.P., B.P.).—(*Blue Vitriol, Bluestone.*) $CuSO_4 + 5H_2O$. Soluble in 2.6 water. *Dose:* As astringent, 0.008 to 0.03 Gm.; as emetic, 0.12 to 1.2 Gm. (1/8 to 1/2 grain). Local: 1/2% to 10% solution.

* Not official.

The most important preparations are marked ⁂.

⁂ *Zinci Sulphas* (U.S.P., B.P.).—(*White Vitriol.*) $ZnSO_4 + 7H_2O$. *Dose:* Emetic, 0.6 to 2 Gm. (10 to 30 grains). Local.

⁂ *Zinci Sulphocarbolas* (U.S.P., B.P.).—$Zn(C_6H_5SO_4)_2 + H_2O$. Freely soluble. Local.

Zinci Chloridum (U.S.P., B.P.).—$ZnCl_2$. Local.

Liquor Zinci Chloridi (U.S.P., B.P.).—50%. Local.

Zinci Carbonas Præcipitatus (U.S.P.).—Insoluble. Local.

⁂ *Zinci Oxidum* (U.S.P., B.P.).—ZnO. Insoluble. *Dose:* 0.06 to 0.03 Gm. (1 to 5 grains).

Locally as dusting-powder and in ointments:

⁂ *Unguentum Zinci Oxidum* (U.S.P.).—20% (with Lard).

⁂ *Unguentum Zinci* (B.P.).—15% of oxid.

Oleatum Zinci Oxidi (U.S.P.).—5%.

XVI. MERCURY.

I. ACTION.

Mercury, unlike the other metals, has a strong specific *toxic action on protoplasm.* It is poisonous not only to the higher plants and animals, but also to lower organisms, and enjoys great germicidal power. It owes this toxicity to a great affinity for nitrogenous molecules.

1. **Absorption.**—The albuminates which are formed in this manner are quite soluble under the conditions of the body—*i. e.*, if a certain amount of sodium chlorid and of alkalinity exists. In consequence, it is *readily absorbed* and transported, differing very conspicuously from other metals in this respect. Further, whilst most metals are almost innocuous in the free state, *metallic mercury* is fairly toxic; its distribution and absorption are favored by the fact that it is liquid and volatile and oxidizes very readily.

The mercury compounds are absorbed from all surfaces. On this rest the mercurial treatments by fumigation and inhalation. Many cases of mercury-poisoning have also occurred from flushing out large cavities with mercuric solutions. The absorption from serous surfaces is very rapid.

2. The **excretion** of mercury occurs to some extent by the urine, but mainly by the intestine; also to some degree by saliva, sweat, and milk. The excretion by the kidneys begins in about two hours after the administration, but it lasts for a long time, and may be demonstrated as late as six months after the administration has been entirely stopped.

With small amounts this excretion causes no pathologic

The most important preparations are marked ⁂.

changes in the kidneys; but if long continued it gives rise to interstitial and glomerular nephritis. Large amounts, on the other hand, occasion a parenchymatous nephritis with glycosuria. The relative quantity of mercury excreted by this channel is increased by the inflammatory changes.

Potassium iodid is said to favor the excretion, just as in the case of lead, but there is not much positive evidence on this point.

3. Fate in Body.—Whilst the elimination of mercury is a slow process, it disappears quite rapidly from the blood, being fixed in the tissues.

Its distribution is much the same as that of lead. It is found especially in the kidneys, to a less extent in the liver, and frequently in the intestinal walls. When taken as vapor it is also found in the lungs. In other organs it is seen only in acute poisoning. It passes through the placenta only when given in very large doses, probably after injuring the vessels. The mercury which has been stored is quite firmly fixed to the non-digestible nuclein residue, favoring the view that it is deposited in the nuclei.

II. TOXICOLOGY.

1. Etiology.—The chances for accidental chronic poisoning with mercury are not nearly so great as with lead, since the metal is much less widely used in the arts. On the other hand, it adheres more persistently to the skin, and is more readily absorbed and more toxic, so that a much less number of those exposed escape poisoning. The most frequent cause of mercury-poisoning was formerly the excessive and injudicious medicinal use of this metal.

The mercury existing in the amalgam used for filling teeth seems to be so firmly combined that it does not cause poisoning.

When injected directly into the blood-vessels the organic (non-ion) mercury preparations act more violently than the inorganic. Although mercury, like other metals, does not act until it has been converted into ion form, the organic compounds are distributed more quickly throughout the body and are readily decomposed.

2. Actions in Acute Poisoning.—(a) The *phenomena of the general poisoning by intravenous injection* consist in a very marked *fall of blood pressure*, due to a direct paralyzing action on both the **heart** and the **blood-vessels.** The former involves both ganglia and muscle.

(b) Mercury, however taken, has comparatively little effect on the **central nervous system,** especially in acute poisoning, the only symptoms which are noticed being secondary to the fall of blood pressure. *Consciousness* is usually preserved to the end. In chronic mercury-poisoning there is sometimes a noticeable tremor—*tremor mercurialis*. This is probably central in origin; as also a heightened psychic irritability, often seen—the so-called *erethismus*. Sometimes, however, there is instead a *dulling* of the faculties. Mercury, like lead, may also produce *peripheral neuritis*, but much later than in the case of lead-poisoning.

(c) **Local Action.**—The general effects are largely overshadowed by the symptoms arising from the *local action*, which consists of a chemic irritation or corrosion:

1. These are most prominent in the alimentary canal, even when mercury has been given by any other channel—by inhalation or by hypodermic or intravenous injection.

They may be due in part to the paralysis of the capillaries, but are mainly due to direct chemic corrosion, since the metal is largely excreted through this channel.

The result is a peculiar *gastro-enteritis*. It begins in the upper portion of the alimentary canal. There is an early *stomatitis* leading to ulceration, and this may extend so deep as to affect the bones, producing *necrosis of the jaw*. Increased *salivation* is a prominent symptom. It is probably due to the excretion of the mercury through the salivary glands.

The gastro-enteritis is, however, most violent in the lower portions of the intestine, and the symptoms bear a close resemblance to those of *dysentery*. The anatomic lesions—ulceration of cecum—are also similar.

2. The excretion of mercury through the *skin* produces various *skin diseases;* the excretion through the kidneys, as has been said, nephritis. There is frequently a *formation of lime crystals* in the lumen of the tubules and possibly in the cells themselves. No explanation for this can be given.

3. **Course of Poisoning.**—The *fatal dose* is 0.18 Gm. Death may take place inside of half an hour, from collapse. More usually, however, the symptoms last several days; and death takes place from the lesions of the intestinal canal.

The acute poisoning may pass into the chronic form—*i. e.*, a single dose may be capable of producing chronic mercury-poisoning—since the mercury is excreted with such extreme slowness.

4. **Treatment.**—The *treatment of acute mercury-poisoning* will ordinarily be directed against the gastro-enteritis. The object will be to prevent the poison from coming in contact

with the cells of the intestine, and also to convert it into a less irritant form. Since the corrosive and irritant action is due to its combining with nitrogenous material, it can be much lessened by the artificial introduction of such material.

The ordinary antidotes are *white of egg* and milk, which fulfill all these indications. The resulting compounds must of course be promptly removed by emetics or lavage, else they will be absorbed and produce general poisoning. One must be cautious not to introduce any common salt into the stomach as long as mercury is present; for this would increase the solubility of the latter.

III. CHRONIC MERCURY-POISONING.

(a) Chronic mercury-poisoning affects **metabolism** profoundly, producing cachexia. There are also *fatty degenerations* of the various organs, as in the case of arsenic or lead-poisoning. An occasional consequence of mercury-poisoning is *diabetes*. On the other hand, mercury is sometimes beneficial in diabetes if this is of syphilitic origin.

The *chemic study* of these metabolic effects is very inconclusive and difficult, on account of the extensive action of mercury on the alimentary canal and upon the kidneys.

(b) It has been claimed that mercury produces a **rarefaction of bone.** This is undoubtedly found in a great many cases of chronic mercury-poisoning, but so far it has not been possible to exclude syphilis as the cause of the rarefying osteitis. It is quite conceivable, however, that mercury has such an action; for the amount of lactic acid in the blood is markedly increased by it, and this might effect solution of the lime salts.

(c) It was formerly claimed that mercury possessed a marked *cholagogue* action. But it has been demonstrated on biliary fistulæ that the flow of bile is not increased.

The green color of the stools, on which this belief was based, is explained by the lessening of the putrefactive changes which are responsible for the conversion of the green bile pigments into those of the feces.

(d) Very small doses of mercury may have the same *beneficial effect upon metabolism* as small doses of arsenic, and probably act in much the same manner. The patient may increase in weight, and the number of red blood-corpuscles may rise, etc.

(e) The **treatment of chronic mercury-poisoning** is the same as that of all chronic metal-poisoning, the object being to favor the elimination of the metal by all possible channels.

As has been said, it is claimed that potassium iodid hastens this elimination, and this has not been disproved. Hygiene is of great importance. For the stomatitis and salivation cleanliness of the mouth and washing with alum or potassium chlorate are very efficient. The prophylaxis in factories where mercury is employed is the same as in the case of lead.

IV. THERAPEUTICS.

1. The use of mercury in **syphilis** rests entirely upon an empirical basis.

We do not even know whether its action is due to specific toxicity for the virus of syphilis or whether it is due simply to the general effects upon metabolism. The former seems to be the case.

Although the usefulness of mercury in syphilitic disorders had up to recent years been a subject for much animated discussion, there appears to be at present no reason to doubt that it is not only palliative, but curative, in the secondary stage of syphilis, congenital as well as acquired; whilst it is useless in the first and third stages.

The first stage is best treated expectantly, the third with iodids. (See p. 563.) The other forms of treatment—sweating, diet, other metals (gold, etc.), sulphur-baths, and the various vegetable antisyphilitics—either act by supporting the mercury or have been discarded entirely.

The mercurial treatment offers the greatest chances of success if it is *begun early* in the disease. In order to be of any permanent benefit it must be *continued for a considerable time*—several years—long after the symptoms have entirely disappeared. When used in this way there can be no doubt but that it frequently effects a *permanent cure*. The dose should never be kept at a point which would cause local symptoms.

2. The best method of **administration,** by the stomach, is to begin with small doses—perhaps one-third of the full dose—and increase these gradually—say 10% every day—until the first tenderness of the gums appears. The dose should then be cut down to half of that taken at this time and continued without further change.

The prolonged administration of mercury offers serious difficulties on account of its irritant action. Given by mouth it is very apt to produce a gastro-enteritis, much more easily than when it it is given by other channels. Since the irritation is due to its combination with the cell-proteids, this may be largely avoided by administering it in the form of proteid compounds—the albuminate or peptonate. The iodids possess some advantage over the chlorids in that they are more easily decomposed in the body. Whatever form is given, the patient should be placed upon an easily digested but nutritious diet. The state of the bowels should be carefully attended to. The mercury may also be introduced by other channels, but all have drawbacks.

The *intramuscular injection* is extremely painful and may cause sloughing. The pain is less if sodium chlorid is added to the mercuric chlorid. It may also be diminished by using non-irritant combinations—the peptonate or albuminate dissolved by the aid of sodium carbonate or chlorid; or mercuric benzoate with sodium benzoate.

For *inunction*, the mercury, usually in the form of a salve, is rubbed *into* the skin—*not* smeared over it. A piece of the ointment is rubbed into the surface of the skin until the mercury has disappeared. A new surface is taken each day, the round of the body being made in about six days. The *blue salve* is the most popular preparation. The officinal article may be improved upon by more thorough emulsification with soaps. The absorption of the ointment, as well as of the vapor in fumigation, can be rendered much more efficient by preceding it by a thorough diaphoresis. It is quite immaterial whether this be attained by teas, by hot baths, medicated or not, or by other means. For *fumigation* a gram of calomel is volatilized over an alcohol lamp in a closed chamber completely surrounding the patient, with the exception of the head. A rubber or other blanket answers the purpose very well. The *inhalation* is obsolete.

3. **Contraindications.**—Mercury preparations are contraindicated whenever there is cachexia or any chronic disease in which the resistance of the body is lowered; for chronic poisoning is then induced very easily. Nor should it be employed when there is nephritis, nor after the sixth month of pregnancy. Mercury has a somewhat deleterious effect on the course of pregnancy and upon the child.

4. Of **other actions** the *diuresis*, caused by mild irritation from small doses, is used especially in heart disease. The therapeutic uses resting upon its other local effects are discussed elsewhere. (Antiseptic, p. 376; Parasiticide, Chap. XXIX, G; Intestinal, Chap. XXX, D and E.)

V. MATERIA MEDICA.

	SOLUBILITY.	DOSE: Metric.	Apothecaries'.
1. **Metallic Mercury:**			
Hydrargyrum cum Creta (U.S.P., B P.).—(Mercury with Chalk—Gray Powder.)—38% Hg. .	Insoluble.	0.03 to 0.6 Gm.	½ to 10 grains.
⁂ *Massa Hydrargyri* (U.S.P.).—33% Hg.—*Blue Mass, Blue Pill* .		0.03 to 1 Gm.	½ to 15 grains.
Pilula Hydrargyri (B.P.).		0.03 to 1 Gm.	½ to 15 grains.

The most important preparations are marked ⁂.

	Solubility.	Dose:	
		Metric.	Apothecaries'.
⁂ *Unguentum Hydrargyri* (U.S.P., B.P.).—50% Hg. *Blue Ointment*, Mercurial Ointment.			
2. Mercurous Salts:			
⁂ *Hydrargyri Chloridum Mite* (U.S.P.) [*Hydrargyrum Subchloridum*, B.P.]. — (*Calomel.*)—Hg_2Cl_2. This enters into Pil. Catharticæ Comp. and Pil. Antimonii Comp. . .	Insoluble.	0.006 to 0.6 Gm.	1/10 to 10 grains.
⁂ *Hydrargyri Iodidum Flavum* (U.S.P.).—(Protoiodid of Mercury.)—Hg_2I_2. . . .	Almost insoluble.	0.01 to 0.06 Gm.	1/6 to 1 grain.
Lotio Nigra (N.F.,B.P.).—(Black Wash.)—7.5 Gm. Hg_2Cl_2 to 1 liter lime-water.			
3. Mercuric Salts:			
Hydrargyri Oxidum Rubrum (U.S.P., B.P.). *Hydrargyri Oxidum Flavum* (U.S.P., B.P.). } HgO.	Almost insoluble.	0.015 to 0.06 Gm.	1/4 to 1 grain.
Unguentum Hydrarg. Oxid. Rubr.—(10% U.S.P.) (10% B.P.)			
Unguentum Hydrarg. Oxid. Flav.—(10% U.S.P.) (10% B.P.)			
Oleatum Hydrargyri (U.S.P.) [*Hydrargyri Oleas*, B.P.] (2% B.P.) —20%.			
Emplastrum Hydrargyri (U.S.P., B.P.). — 1.2% of Oleate.			
⁂ *Hydrargyri Chloridum Corrosivum* (U.S.P.) [*Hydrargyrum Perchloridum*, B.P.].—*Bichlorid of Mercury.*—*Corrosive Sublimate.*—$HgCl_2$. Mainly for local use.	16 parts (3 parts alcohol).	0.001 to 0.006 Gm.	1/60 to 1/10 grain.

The most important preparations are marked ⁂.

	Solubility.	**Dose:**	
		Metric.	**Apothecaries'.**
Hydrargyrum Ammoniatum (U.S.P., B.P.).—(White Precipitate.)—NH_2HgCl.			
Unguentum Hydrarg. Ammon.—10% (U.S.P., B.P.).			
Liquor Hydrargyri Perchloridi (B.P.).—1 drachm = $\frac{1}{16}$ grain . .		2.0 to 4.0 c.c.	½ to 1 drachm.
Lotio Flava (N.F.) (B.P.).—*Yellow Wash.*—3 parts $HgCl_2$ in 1000 Lime-water.			
Hydrargyri Iodidum Rubrum (U.S.P., B.P.).—HgI_2. Freely soluble in KI	Almost insoluble.	0.001 to 0.006 Gm.	$\frac{1}{60}$ to $\frac{1}{10}$ grain.
Liquor Arseni et Hydrargyri Iodidi (U.S.P., B.P.).—Donovan's solution, 1% of each . .		0.3 to 1.3 c.c.	5 to 20 minims.
Liquor Hydrargyri Nitratis (U.S.P., B.P.).—60% $Hg(NO_3)_2$. Caustic.			
⁂ *Unguentum Hydrargyri Nitratis* (U.S.P., B.P.).—(Citrine Ointment.)—Irritant.			
Hydrargyri Cyanidum (U.S.P.).—$Hg(CN)_2$.	13 parts.	0.001 to 0.006 Gm.	$\frac{1}{60}$ to $\frac{1}{10}$ grain.
Hydrargyri Subsulphas Flavus (U.S.P.) (*Turpeth Mineral.*)—$Hg(HgO)_2SO_4$	Almost insoluble.	0.12 to 0.25 Gm.	2 to 4 grains.
* *Sal Alembroth.*—Two-thirds $HgCl_2$ and one-third NH_4Cl. Less irritant.			
⁂ *Mercury Albuminate.*—Antiseptic [?] dusting-powder.			

XVII. LEAD.

The phenomena of lead-poisoning are characterized by the *independent involvement of very numerous and diverse organs.* Lead, in this respect, occupies a rather peculiar position amongst the metals, and, indeed, amongst all poisons. For whilst so extensive an action suggests the idea of a general toxicity to protoplasm, this does not seem to exist, since lead is comparatively non-toxic to lower organisms. It is a specialized poison; but it is specialized for quite a number of tissues and organs.

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* Not official.
The most important preparations are marked ⁂.

I. ABSORPTION, ETC.—ETIOLOGY OF POISONING.

The action of lead is influenced so greatly by its absorption, retention, and excretion that it will be well to discuss these subjects first.

Lead salts are astringent rather than corrosive. They may cause sufficient corrosion to be absorbed, but this absorption is never sufficient to cause *acute* fatal poisoning from systemic effects. At least, no case is on record in which this has occurred. A very small amount, however, is absorbed fairly readily, in whatever form the lead is given and whether in large or small doses. This is quite insufficient to cause any immediate symptoms. But these traces are excreted extremely slowly, and this ready absorption and slow excretion furnish the conditions for cumulative action.

Lead is perhaps the best example of a poison which is comparatively free from danger in a single dose, no matter how large, but which becomes fatal in the most minute doses, if these are consumed for a sufficiently long time.

In this way it is responsible for very many deaths, many more than arsenic. Lead may be absorbed from any part of the surface of the body—from the skin as well as from the alimentary canal. *Hair dyes* containing lead are a frequent source of poisoning; but the absorption is much greater from the mucous membranes, and the gastro-intestinal tract forms by far the most common way of entrance.

Occasions for the introduction of lead are very numerous. The metal is used extensively in the *arts*, and the workers in these—painters, dyers, type-setters and type-founders, plumbers, etc.—are the most frequent sufferers after lead miners and the working-men in white-lead factories.[1]

But the occurrence of chronic lead-poisoning is by no means confined to these artisans. The metal is so widely distributed that every one is to some extent exposed. Some of the ways in which poisoning has occurred are very surprising. Others are more easily understood. Perhaps the first of these to come to the mind is the lead of *water-pipes*. The opinion amongst medico-legal authorities as to the danger of lead-pipe has varied considerably. But at the present time it seems to be accepted that, if perfectly pure water is allowed to flow through bright and clean lead-pipes, poisoning results invariably. In this case the surface of the lead is changed into a hydrate, and this is sufficiently soluble to cause the intoxication. But the danger is very much less with old lead-pipes as ordinarily used; these have become lined with a layer of lead oxid, $PbO + Pb$. This is quite insoluble, and does not form a hydrate. The chance of solution is still less if the water contains calcium carbonate and carbonic acid. Ordinary lead-pipes would therefore present but little danger. But even then, if the water is allowed to stand a long time in the pipes, some solution is bound to occur. On account of this danger, lead-pipes should be condemned.

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[1] The smoke and fumes from lead factories contain quite a large amount of the metal. This is deposited on the soil and on the surface of plants, and is also taken up into the tissues of the latter. Cases of poisoning have been referred to the milk of cows fed on these.

The employment of lead *vessels for cooking* should, of course, be entirely discarded. *Tinned vessels*, especially tin cans, usually also contain a certain amount of lead in the solder. If the percentage does not exceed a certain limit, the lead seems so firmly combined in the alloy as to prevent its solution even by moderately acid liquids, such as vinegar. If it exceeds this quantity, a certain amount will be dissolved, and will exert its toxic action.[1] The addition of some lead is also necessary in tin-foil, such as is used for wrapping articles of food, to make the tin workable. Here, also, it is harmless if it does not exceed a certain limit. Lead enters into the glazing of *earthenware* vessels, and is contained in many varieties of *glass*; but if it exists entirely in the form of silicate of lead, it presents no danger. All these vessels may be easily tested with sufficient accuracy by allowing vinegar or dilute acetic acid to stand in them for twenty-four hours and then passing a current of sulphuretted hydrogen through the liquid. If there is no precipitate, the amount of lead is below the dangerous limit. It is a somewhat peculiar fact that lead bullets in a wound do not seem to exert the lead action. They probably become oxidized in such a way that none of the metal is absorbed.

The lead is always absorbed in the form of soluble proteid combinations. These may be formed from lead compounds which are perfectly insoluble in water or acids. Even lead sulphate, one of the most insoluble of substances, will be absorbed in sufficient amount to produce poisoning, so that sulphuric acid is useless as a prophylactic.

Excretion.—Lead is excreted by all channels, possibly with the exception of the sweat. The principal path is by the epithelium of the skin and especially of the alimentary canal. It is said that chronic lead-poisoning may usually be detected by painting the skin with sulphid of ammonium, this giving a black color. In painters this is perhaps often due to the adherence of lead to the skin.

The lead is also commonly deposited in the shape of sulphid on the edge of the gums, giving the characteristic "*lead line.*" The *feces* in lead-poisoning also very frequently have a dark color from the action of the H_2S formed in the intestines, upon the excreted lead. It is said that the excretion of lead is very greatly favored by potassium iodid; in what manner is not known.

Retention.—The lead which is retained in the body is stored especially in the liver and other organs, the blood containing only very small traces.[1]

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[1] In Germany, Austria, and some other countries, the lead in solder which comes in contact with food is limited by law to 10%, in tin plate to 1%, and in France only half of this amount is permitted. None of the States in the Union place any limit on this, desirable as it appears from a hygienic standpoint.

There is a very great individual variability in the **susceptibility** to lead-poisoning; with a number of persons exposed to the same conditions, and using the same precautions, some will be violently poisoned and others not at all. This depends perhaps upon differences in absorption and excretion, but anemic patients and persons with low resistance generally are very susceptible.

II. PHENOMENA OF LEAD-POISONING.

The primary symptoms of chronic lead-poisoning consist in local irritation, changes of metabolism, and in nervous phenomena, mainly of central origin.

The systemic actions do not occur in any regular order, so that evidently they do not depend one upon another.

1. The **local irritant action** is seen mainly in acute poisoning.

(a) **Alimentary Canal.** — Lead acetate and most lead preparations have a sweetish astringent *taste.* This is soon followed by the usual *symptoms of irritation in the alimentary canal:* salivation, dysphagia, vomiting, and diarrhea, etc. The vomit is sometimes bloody. The diarrhea is not as profuse in lead-poisoning as it is with most irritant poisons, on account of the astringent action.

The lead salts, like some other metallic salts, form an insoluble coating over the mucous membrane of the intestine, and so prevent the ordinary lead preparations from penetrating and from causing deep corrosion and extensive absorption.

(b) Another evidence of the irritant action of lead is found at the point of excretion; that is to say, in the **kidneys.** Nephritis is a very common consequence of acute lead-poisoning, and an invariable accompaniment of chronic intoxication. In the latter case it may be in part secondary to some of the other effects of the lead: viz., the gout or the arteriosclerosis.

(c) The local irrritant actions upon the alimentary canal and upon the kidneys help to explain the **metabolic changes,** but these are also in part direct, in part secondary to the vascular injury. The chemic changes are rather obscure.

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[1]

Liver	0.03 to 1.00%
Kidney	0.03 " 0.07%
Brain	0.02 " 0.05%
Bones	0.01 " 0.04%
Muscles	0.004 " 0.008%
Blood	traces.

There is a profound *anemia*. This is at first due merely to constriction of the cutaneous vessels; but later there is a diminution of hemoglobin and of the number of red corpuscles. The destruction of these very frequently gives rise to *icterus*. The *intima of the blood-vessels* undergoes fatty degeneration, and this is frequently followed by *arteriosclerosis*. *Fatty degenerations* are also found in other organs: in the kidneys, liver, and other glands. Another expression of the perverted metabolism is the occasional production of *gout*.

Lead always exerts an unfavorable influence upon *pregnancy*. The number of miscarriages in women affected by lead-poisoning is very large; and of the children born, by far the largest proportion die during the first year of life.

2. The effects of lead-poisoning upon the **peripheral nerves** and muscles are very often characterized by the fact that the symptoms appear suddenly, last for quite a short time,—several hours, perhaps,—and then disappear, to recur later.

(a) The most conspicuous of these peripheral effects is **lead colic.**

This is produced as readily by the hypodermic or intravenous administration of lead, as when it is taken by mouth.

It is characterized by violent pains, localized especially near the umbilicus. The abdomen is very conspicuously contracted, even scaphoid. The patient frequently lies on his face, with the fists pressed against the painful region, since pressure relieves the distress.

This colic is caused by the violent contraction of the intestinal muscles. Since this forces the blood out of the vessels of the splanchnic area, the general blood pressure will rise, the pulse will be hard and tense, and the heart will be slowed.

The cause of this contraction must be a *stimulation of the nerve endings*, since it does not possess the peristaltic character of ganglionic stimulation and is entirely abolished by atropin. It is largely relieved by measures which dilate the blood-vessels, for instance, nitrites, so that one is justified in assuming a primary vasoconstriction as one of its causes.

(b) Of **other affections of the peripheral nerves,** *anesthesia* or disturbed sensation of the skin, and more rarely of underlying organs, is conspicuous.

A striking instance of this disturbed sensation is the ***arthralgia saturnina***, a painful affection of the joints and adjacent muscles. The pain is very violent, as in the colic, which it resembles closely. Like this, it appears suddenly, lasts a few hours, disappears, and recurs.

This arthralgia is not seen in animals; but these seem to be much less sensitive to articular pain than man. They also show very little distress if acute arthritis is produced by uric acid injection.

Neuralgias occur occasionally. They have perhaps several explanations: In some cases they are due to a peripheral neuritis, in others to an action on the central nervous system.

(c) The actions on the **motor system** consist in neuritis, paralysis, and atrophy. The seat of this action has given rise to considerable discussion. It has been placed in the central nervous system, in the peripheral nerves, and in the muscle cells. The last two are probably the usual seat, but the central nervous system may undoubtedly participate in some cases.

The action of lead upon *isolated muscle* is quite characteristic. There is at first an increase in the ease with which the muscle is fatigued, and the fatigue curve presents some very peculiar changes. In the normal fatigue curve the height of the successive contractions decreases in a perfectly regular manner; if a line is drawn joining the summits of the contractions, this is practically straight. But if fatigue is produced in a muscle poisoned by lead, the line is extremely irregular. One contraction will be very low, another high, etc. It will also require a less number of contractions to produce complete fatigue than in the case of normal muscle.

In chronic poisoning in the intact animal *early fatigue* is also a prominent symptom. This gives way to *paralysis*.

The onset is slow. The muscles first become insensitive to voluntary stimulation and later to electric. At this time the reaction of degeneration sets in; that is to say, the muscle is hypersensitive to galvanic, and less sensitive than normal to faradic stimulation.

The paralysis is followed by total *atrophy*.

The **heart** may be similarly affected, and this quite early in the poisoning; this is the case especially if the poison is injected directly into the blood.

The action upon the *peripheral motor nerves* is probably quite similar to the direct muscular action.

This paralysis of the extensor muscles has been advanced to explain a very common phenomenon of lead-poisoning, the **drop wrist** or lead wrist.

Others, however, attempt to explain it by active contracture of the opposing flexor muscles. It is not unlikely that both have a part in the explanation.

The contracture begins at the metacarpo-carpal articulation of the two middle fingers, then the two outer fingers and the thumb, and then the wrist.

3. The effects upon the **central nervous system** constitute what is called *encephalopathia saturnalis.* They are exerted especially on the cortex. There is first irritation, which is followed by paralysis. The effects are both sensory and *motor,* but particularly the latter. They begin with contractures, then choreic movements, then possibly generalized *convulsions.*

The convulsions which are seen in lead-poisoning are not always due to the lead itself, but sometimes to the nephritis; *i. e.,* uremic.

Later the motor stimulation gives place to paralysis.

On the part of the *mental and psychic faculties* there is delirium, then depression, and in the last stages, coma. The latter may also be uremic. Lead-poisoning is claimed as a contributory factor of insanity.

It is said that in very prolonged cases of lead-poisoning, the anterior columns of the spinal cord show histologic degenerations. A case of criminal poisoning is known where small doses were administered during six months. The symptoms were described as persistent vomiting, constipation, and colic, followed by paresis and epileptiform convulsions. Symptoms similar in all respects to the above may be evoked in animals by the injection of organic lead preparations such as lead-triethyl.[1]

III. TREATMENT OF LEAD-POISONING.

In acute lead-poisoning it is well to administer a sulphate, so as to render the lead as far as possible insoluble, and then to remove it quickly by means of an emetic.

In chronic lead-poisoning removal of the lead is also one of the main indications. Hot baths are efficient for this purpose, as also the administration of potassium iodid in fairly large doses. For the rest, the treatment must be purely symptomatic: For the colic, belladonna, opium, and the nitrites; for the prevention of paralysis and atrophy, strychnin, massage, electricity, etc.

Prophylaxis is of the greatest importance. The public should be thoroughly educated to the insidious dangers of lead, and the chances of poisoning carefully guarded against. The sources of danger—lead-pipes, etc.—should be eliminated. Tin cans, foil, etc., should be frequently examined by authorized persons. Special precautions are required in lead factories and in exposed trades. Since the main channel of poisoning is by the mouth, extreme cleanliness should be encouraged and made possible by liberal facilities for washing. Food should not be permitted on the premises, and the clothing should be changed before leaving the works. More stringent laws are greatly needed in this connection.

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[1] The metal Thallium resembles Lead in its action. The acetate has been used in doses of 0.005 to 0.01 Gm. per day, against the night-sweats of phthisis. It caused neuritis, and its use is not justified.

IV. THERAPEUTICS.

The therapeutic importance of lead rests entirely upon its local astringent actions. It should never be taken internally and should never be continued for a long time. In the latter case it may be in part secondary to some of the other effects of the lead: viz., the gout or the arteriosclerosis.

V. MATERIA MEDICA.

(Lead preparations should not be used internally, and only for a short time externally.)

⁂ *Plumbi Acetas* (U.S.P., B.P.).—(*Sugar of Lead.*)—$Pb(C_2H_3O_2)_2 + 3H_2O$. Soluble in 1.8 parts water. *Dose:* 0.03 to 0.3 Gm. (½ to 5 grains). Externally against ivy-poisoning.

Liquor Plumbi Subacetatis (U.S.P.) [—— *fortis*, B.P.] (*Goulard's Extract*).—25%. Used only to prepare the lead-water.

⁂ *Liquor Plumbi Subacetatis Dilutus* (U.S.P., B.P.).—(Lead water.)—¾%. Externally.

Unguentum Plumbi Acetatis (B.P.).—4%.

Suppositoria Plumbi Composita (B.P.).—Each contains 3 grains of lead acetate and one grain of opium.

Plumbi Carbonas (U.S.P., B.P.).—*White Lead.*—$(PbCO_3)_2Pb(OH)_2$. As dusting-powder and in:

Unguentum Plumbi Carbonatis (U.S.P., B.P.).—10%.

⁂ *Emplastrum Plumbi* (U.S.P., B.P.).—*Diachylon* or *Lead Plaster.*—A lead-soap, made by boiling lead oxid (Litharge) with Olive Oil.

XVIII. PHOSPHORUS.

I. VARIETIES.

The element phosphorus exists in two forms, the red and yellow. The former is non-volatile, and is insoluble in water or oil, is not absorbed, and is therefore not toxic. The yellow or ordinary phosphorus, whilst also insoluble in water, is very volatile, and penetrates the tissues with ease, especially when in finely divided state, or when dissolved in fats. Phosphorus acts as such, the compounds being harmless and having a totally different action.

The most important preparations are marked ⁂.

II. SUMMARY OF ACTIONS.

1. Direct paralysis of cardiac muscle.

2. Changes in metabolism, consisting in an increased decomposition of proteids; diminished oxidation; fatty infiltration of epithelium and muscle, with subsequent connective-tissue infiltration; increased formation of sarcolactic acid; modifications in bone-formation and in the blood.

III. DETAILS OF ACTION.

1. The one acute and direct action of phosphorus is on the **heart.** Large doses paralyze this organ, acting apparently on the muscle-fibers. (Phosphorus has no action on muscle-nerve preparations.) There is consequently a fall of blood pressure and eventually cessation of cardiac action.

2. **Action on Metabolism.**—This is the most interesting feature of phosphorus-poisoning from a scientific standpoint, being almost unique. It occurs in chronic poisoning, or as a secondary process after a single larger dose.

It cannot be said that the process is very thoroughly understood. It may be reduced to an increased metabolism of nitrogen, and a diminished oxidation. But what relation these two processes bear to each other cannot be stated.

(A) **Nitrogen Metabolism.**—This is very greatly increased, as much as 300%. The change is not only quantitative, but also qualitative; *i. e.*, the nitrogenous metabolites are not in the normal ratio. The urea is not nearly so much increased as the others, and may even be less than normal. It is to a large extent replaced by ammonia. This may be attributed to an increased production of sarcolactic acid. But, in addition, some of the N is excreted in the urine in less completely oxidized form, as leucin, tyrosin, and peptone-like bodies.[1]

(B) A rise in the metabolism of cell-proteids always causes **fatty changes** of cells. (This is also seen with phloridzin, arsenic, antimony, many volatile oils, alcohol group, benzol, phallin, etc.) In the case of phosphorus, the main effect falls upon the liver cells, but practically all other cellular organs are involved: muscle, skeletal, and cardiac; kidneys; blood-vessels; epithelium of stomach and intestine, etc. The fatty changes are preceded by "cloudy swelling," which is probably an intermediate stage. They are followed by proliferation of interstitial connective tissue (cirrhosis).

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[1] These are formed principally in the liver, and are perhaps due to an increase of the normal autolytic ferment action of this organ (Jacoby). Similar changes occur in acute yellow atrophy.

The question is still under discussion as to whether the fatty changes are infiltrations or degenerations; whether the fat is merely transported from other portions of the body, or formed *in situ*. The bulk of the evidence is in favor of infiltration. There seems to be no doubt that the total amount of body-fat in the frog is not increased; and it is stated that the fat in the phosphorus-liver does not differ in composition from the body-fat. Since the proteids are diminished, as also the glycogen, the hypothesis is not improbable that the fatty changes in this, as in other conditions, are the expression of starvation. The cell, on being deprived of its ordinary food, draws on the fat of adipose structures to supply the deficiency.

(*a*) The changes in the *Liver* consist, then, in increase of fat (three to four times the normal amount); diminution of glycogen; increased formation of ammonia, and of leucin and tyrosin.

There are also marked changes in the *bile*. At first there is an increased formation and excretion of bile pigment. This is perhaps in part due to a destruction of red blood-cells, in part to an increased activity of the hepatic epithelium. Later the bile-pigments are retained, leading to *icterus;* whilst a thin fluid is excreted, which is probably mainly mucus. The suppression of the bile secretion is presumably due to occlusion of the bile capillaries; at first, through the fatty enlargement; later, through the cirrhosis.

(*b*) The degeneration of the *muscles* leads to debility; of the *heart*, to weakening of the circulation; of the *kidneys*, to albuminuria, which is never very severe.

(*c*) Degeneration of the *blood-vessels* leads to loss of elasticity and to capillary hemorrhages. It may also be in part responsible for some of the other changes. The *blood* is also affected directly; it becomes less coagulable and the red corpuscles are decreased in the dog (not in rabbit and man ?).

(*d*) The degeneration of the *cells of the gastric and intestinal mucosa* explains the abdominal pain, vomiting, and occasional diarrhea. These occur equally readily after hypodermic injection, so that they are not due to a local action, but rest on the metabolic changes.

(C) **Other Effects.**—The use of O and the excretion of CO_2 are diminished.

The P_2O_5 *in the urine is increased*, but much beyond the amount of P administered. This is only another expression of the increased proteid metabolism. The NaCl is diminished on account of the anorexia.

The *growth of young bones* is affected in a peculiar manner, somewhat as with arsenic, the cancellous tissue tending to become compact. The necrosis of the jaw, often seen in the operatives of ill-ventilated match factories, is referred by some authors to the phosphorus itself; by others, to the lower oxidation compounds.

The *central nervous system* is not affected directly.

Phosphoretted Hydrogen causes a very similar intoxication.

IV. TOXICOLOGY.

1. **Etiology.**—Phosphorus is quite accessible in the form of matches or phosphorus rat paste, so that poisoning, accidental or suicidal, is not at all rare. Chronic poisoning of a somewhat different character is seen from its fumes, in phosphorus and match factories. This, as well as the poisoning by matches, has been very greatly diminished since the introduction of amorphous (red) phosphorus.[1]

Phosphorus burns are no more dangerous than other burns of similar extent and do not exhibit any of the symptoms of phosphorus-poisoning.

2. The **symptoms** appear usually only after some hours, and begin with burning and pain in the abdomen, and vomiting. The vomit has the odor of garlic, and is luminous in the dark. The patient then usually improves greatly, and appears normal for two or three days. At the end of this time, icterus makes its appearance, together with abdominal pain and tenderness; emesis, often bloody; and diarrhea. The area of liver-dullness is increased. There is considerable muscular weakness and pain, and general prostration; the pulse is small and quick. The urine contains bile, albumin, leucin, tyrosin, an abnormal amount of ammonia, etc., sometimes blood. Hemorrhages occur in many different situations. There is usually a fever, sometimes abnormally low temperature. This condition lasts five to eight days, when the patient usually dies of heart failure. Recovery is possible, however, even when the symptoms are very severe.

The *fatal dose* is 50 mg.; but 13 mg. cause very grave intoxication.

3. **The treatment** consists, in the early stages, in the

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[1] The first phosphorus friction matches were made by Dérosne, Paris, in 1816, but they did not become practical until 1833, when processes for their manufacture were invented in several countries. These all employed yellow phosphorus; each match contains 3 to 5 mg., so that 16 would be fatal for an adult.

The more modern amorphous phosphorus matches contain, besides this, some oxidizing agent ($KClO_3$, KNO_3, chromate or oxid of Mn, Pb, Fe) and paraffin, glue, etc.

The "safety matches" have no phosphorus on the sticks, which are usually headed with Sb_2SO_3, $KClO_3$, and glue; the phosphorus is here on the friction surface coating the box.

administration of $CuSO_4$ as emetic: the Cu is precipitated in metallic form on the P globules and retards their absorption. The stomach should then be washed with 0.2% $KMnO_4$ or with H_2O_2. Old spirits of turpentine in doses of 1 to 2 c.c. should be given several times a day for some days. All these measures are for the purpose of oxidizing the phosphorus; the last acts even after the P is absorbed. Oils and fats of all kinds must be avoided. Alkalies are useful to neutralize the excessive sarcolactic acid. For the rest, the treatment must be symptomatic.

A peculiar *necrosis of the jaws*, as observed in match factories, begins with salivation, suppurative ulceration of the gums, and ends in a very profound periostitis, involving the whole jaw. It usually starts in carious teeth. The lower jaw is more often affected. The only treatment is excision of the diseased bone.

V. THERAPEUTICS.

The only rational indication for phosphorus is in deficient lime deposition in bone, as in rickets, osteomalacia, and ununited fracture. However, the evidence in regard to its benefits is not very conclusive, and it is certainly a very dangerous remedy. The first effects are to be seen in about four weeks. It must be omitted if gastric symptoms appear.

Its use in diseases of the nervous system—alcoholism, sexual exhaustion, neuralgia, etc.—is not supported by any pharmacologic action, nor by clinical results; nor has its use in chlorosis any scientific basis.

VI. MATERIA MEDICA.

Phosphorus (U.S.P.).—*Dose* (in Preparations): 0.0005 to 0.003 Gm. ($\frac{1}{100}$ to $\frac{1}{20}$ grain).

Pilulæ Phosphori (U.S.P.).—Each contains 0.0006 Gm. ($\frac{1}{100}$ grain). *Dose:* 1 to 5.

Pilula Phosphori (B.P.).—2%. *Dose:* 0.06 to 0.1 Gm. (1 to 2 grains).

Spiritus Phosphori (U.S.P.).—0.12%. *Dose:* 0.5 to 2.5 c.c. (8 to 40 minims).

⁂ *Elixir Phosphori* (U.S.P.).—0.025%. *Dose:* 2 to 10 c.c. (½ to 2½ drachms).

⁂ *Oleum Phosphoratum* (U.S.P., B.P.).—1% in Almond Oil. *Dose:* 0.06 to 0.3 c.c. (1 to 5 minims).

* *Elixir Phosphori et Nucis Vomicæ* (N.F.).—Each teaspoonful = 2 minims Tinct. Nux Vomica and $\frac{1}{30}$ grain Phosphorus.

The most important preparations are marked ⁂.

VII. HYPOPHOSPHITES.

Although these salts are popularly supposed to improve nutrition in anemia and beginning phthisis, there is absolutely no scientific foundation for this belief.

MATERIA MEDICA.

The dose of the dry salts is 0.12 to 1.2 Gm. (2 to 20 grains). They are soluble in 1 to 8 parts of water.

Calcii Hypophosphis.—$(CaPH_2O_2)_2$ (U.S.P., B.P.).
Sodii Hypophosphis.—$NaPH_2O_2 + H_2O$ (U.S.P., B.P.).
Potassii Hypophosphis.—KPH_2O_2 (U.S.P.).
Ferri Hypophosphis.—$Fe_2(PH_2O_2)_6$ (U.S.P.). Insoluble.

⁂ *Syrupus Hypophosphitum* (U.S.P.).—*Dose:* 4 to 8 c.c. (1 to 2 drachms).

Syrupus Hypophosphitum cum Ferro (U.S.P.).—(1% Iron Lactate.) *Dose:* 4 to 8 c.c. (1 to 2 drachms).

* *Syrupus Hypophosphitum Compositus* (N.F.)—Each teaspoonful contains ⅛ grain each Hypophosphite of Iron and Mn; 1/16 grain Quinin Hydrochlorate; 1¼ min. Tr. Nux Vomica.

CHAPTER XXVIII.

IRRITANTS, CORROSIVES, AND ASTRINGENTS.

(A) GENERAL PHENOMENA.

THE symptoms produced by poisons and drugs after their absorption present a great variety, according to the organs on which they act; each organ reacting by various modifications of its own peculiar function.

In the case of a strictly local action, produced at the point of application, the conditions are much more simple. Only a few structures need be considered,—the skin and mucous membranes,—and these have essentially an identical structure. Their functions also are comparatively few and easy to oversee. For these reasons, there are many phenomena which hold true of all local irritant poisons, and which may be studied once for all; these present only minor modifications in individual cases. They resemble in the closest manner those of inflammation produced by any other cause.

These local irritants act by producing necrosis of protoplasm, and this by a purely chemic action. With few exceptions, they cause coagulation or other profound chemic changes of proteids in the test-tube. Indeed, any substance which produces such changes is an irritant. And when one considers the extreme sensitiveness of proteid to reagents, the extreme readiness with which it undergoes chemic or physical changes, it will be apparent that practically every known substance—even water—may exert irritant actions under proper conditions. In the substances which we have studied, we have rather neglected this local irritation, since it was generally overshadowed by other actions. With other drugs, however, the local phenomena form by far the most conspicuous, or even the only, symptoms.

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* Not official.
The most important preparations are marked ⁂.

I. PHENOMENA OF IRRITATION.

1. These can be studied very typically on the **skin.** The first degree of irritant action is shown in an arterial and capillary hyperemia, at first active, later passive. This constitutes the "dermatitis erythematosa" of the dermatologists. Or, speaking pharmacologically, it constitutes **rubefaction,** and the agents which produce it are therefore called rubefacients. The congestion is accompanied by sensory stimulation—by itching or pain.

If the irritant action does not go any further than this, resolution takes place without leaving any lesions, simply by a return of the vessels to normal. Usually the upper layers of the skin are desquamated.

If the action is stronger than rubefaction, it may go into vesication or pustulation. **Vesication** occurs if the inflammatory action results in the formation of an exudate greater in amount than can be carried off by the lymphatics. Every hyperemia is, of course, accompanied by an increase of exudation, but up to a certain amount, as in rubefaction, this is readily reabsorbed. When this limit is exceeded, an actual, visible, effusion results. This liquid will accumulate in the parts of the tissues offering the least resistance to distention. In the case of the skin, it penetrates readily through the lower layers of the rete Malpighii, but is arrested by the impermeable stratum corneum. It is therefore confined between the upper and lower layers of the rete Malpighii, and separates them, in this way causing blisters or vesicles. The agents which produce these are called *vesicants* or *epispastics*.

Resolution takes place in these cases without loss of tissue, by the formation of a new stratum corneum from the remaining rete Malpighii.

If the overlying and separated layers of epidermis are removed, there is much chance of infection, the lower layers of the rete Malpighii offering but little resistance. In this way there may be a loss of substance from secondary infection. The sensory stimulation of this vesication is still stronger than that of rubefaction.

If the inflammation, instead of leading to an effusion of liquid, leads to an emigration of leucocytes, it produces **pustulation**, the agent being called a *pustulant*. This depends to some degree upon the violence of the inflammation, a more profound irritation being required to produce an emigration of leucocytes than what suffices to cause an effusion. But to some extent it is also a specific property of the pustulant. Certain vesicants never produce pustulation, whilst certain pustulants do not vesicate. The pustulant action is probably the more common when there is a special involvement of the cutaneous glands. Indeed, it is usually confined to these, and is but rarely diffuse, for the reason that both the irritant and the bacteria can penetrate more readily at these points. In other cases, as with tartar emetic and the bromids, the acid secretion of these glands dissolves or liberates the irritant agent.

In pustulation there is necessarily always some loss of tissue and scar formation. Sensory stimulation is still stronger than in the case of the vesicants.

If the inflammation exceeds this degree, it leads to necrosis of the cells; and **corrosion**, or *cauterization*, results. This is the last degree of the inflammatory action. Destruction of tissue by irritants may be the result either of inflammatory necrosis or of a direct chemic action.

The stronger acids and alkalies, as also bromins and some of the metallic poisons such as arsenic and mercury, form soluble compounds with proteids, and produce solution in this manner. Others, as most of the metallic, saline, and organic irritants, kill the cells by precipitating their proteids.

The chemic destruction of tissue is always preceded by this inflammatory necrosis. Chemic cauterization will therefore always show three areas: The first, situated at the depth and periphery of the ulcer, is simply an area of inflammation and hyperemia. Then follows a layer of necrotic tissue, the result of the inflammatory action; and last, a layer in which the chemic cauterization results in solution of the cells which have already been killed by the inflammatory process. These three—hyperemia, inflammatory necrosis, and chemic solution—are to be considered as successive stages in the same action; and by proper dilution, the second or first degree of action may be obtained without the succeeding stages.

The strength of action, for the same substance, is a matter depending on the concentration, rather than on the absolute amount—just as a gram of $MgSO_4$ in solid form introduced into a solution, may precipitate all its globulin, whilst an unlimited quantity may be added in 5% solution, without any such effect.

When the chemic corrosion leads to a loss of substance, the inflammatory exudate will be poured on the surface, where it will coagulate. This coagulum, together with the products of the chemic action of the irritant upon it and upon the cells,—the albuminates, etc., which are formed,—constitute the "scab" or "**eschar.**" Its character will vary with the nature of the chemic products entering into it:

If the irritant has a solvent action on proteids, as is the case with alkalies, the scab will tend to be liquid. If, on the other hand, the combination between the proteid and the irritant is insoluble, as with most metals, the scab will tend to be hard. This is of considerable importance, since it determines the depth of action of the corrosive agent. If the scab is soft, the chemical will penetrate it, and its action will not be limited; it will spread and extend deeply. On this account the alkalies, for instance, are not practical for the purpose of cauterization. If, on the other hand, the scab is solid, it prevents deeper penetration, so that the action can be very easily confined to the desired areas.

In the case of actual destruction of tissue by cauterization, resolution will take place, as after inflammatory necrosis, by scar-formation.

2. Certain differences in detail will be seen when irritants are applied to other surfaces than the skin; for instance, to the **mucous membranes.** These are readily explained by anatomic peculiarities. There will, for instance, be less tendency to vesication, since the epithelium is not impermeable, as it is in the skin. Nor will there be any chance of the distinct pustulation, which depends upon the cutaneous

glands. On the other hand, the mucous glands will be stimulated to an increased activity, producing "*catarrhal*" *conditions.*

The *tongue* reacts to different forms of mild irritation in a somewhat specific manner, which seems to have its basis in the papillary arrangement. These differences, constituting the various kinds of "coatings," etc., are of some diagnostic importance in disease. But they can all be reduced to the ordinary phenomena of moderate inflammation: hyperemia and proliferation, or necrosis and desquamation, of epithelium. The epithelium of the mouth is sufficiently impermeable to allow of vesication, although less readily than the skin.

In the **stomach and intestine** the action of irritants will produce physiologic as well as anatomic phenomena, comprised under the name of *gastro-enteritis* (see p. 657). There will be diarrhea and vomiting. These may, indeed, occur without actual destruction of tissue. When cauterization has taken place, the evacuation will be tinged with blood, which may be altered by the reagents. Acids, *e. g.*, will convert it into the dark-brown acid hematin, giving rise to the "coffee-grounds" vomit. A further complication may arise if the corrosive eats its way through the intestinal wall, producing peritonitis. Destruction of tissue in this situation is very apt to produce *severe shock.*

3. **Kidney and Liver.**—None of the irritants exert their irritant action upon the body at large. Most of them are not at all absorbed, and when absorption does take place, they are too greatly diluted to act anywhere except in the liver, and especially in the **kidney.** All irritant substances will produce nephritis if they are absorbed. Many of them will cause irritation of the liver-cells, leading to fatty degeneration, and later to cirrhosis, precisely as in the case of alcohol.

4. **Respiratory Passages.**—If an irritant poison is *volatile*, its main effects may fall upon the *respiratory passages.* The general phenomena will be those of acute laryngitis, bronchitis, or pneumonitis.

5. There appear to be some **specific differences** between the different irritants as to the strength of their action in different situations. Some, for instance, seem to act especially on the alimentary canal, and to a very small extent on the skin. This is probably connected with differences

of absorbability. A drug which cannot penetrate the skin, cannot, of course, act upon it. It will be remembered that the epidermis is impermeable to most substances. In order to penetrate, these must be either fatty, like croton oil; or volatile, like turpentine; or they must actually destroy the epidermis, like caustics.

All irritant substances will act to some extent as **antiseptics.** They will destroy the protoplasm of bacteria, just as they do that of tissue cells.

II. PHENOMENA OF ASTRINGENT ACTION.

When the solvent action of the chemical is very small and its precipitant action very large, the course of events is quite different from that described. It leads in this case to what is called an "*astringent action.*" The astringent action is always preceded by a small amount of inflammatory action. But this, instead of passing on to necrosis of tissue, leads to a diminution of the already existing inflammatory process. An astringent action may be defined as one which lessens the typical processes of inflammation,—that is, the congestion and the permeability of the capillary walls,—and leads to the absorption of the effusion. The astringents also produce a visible *wrinkling of the mucous membranes* to which they are applied, and lessen the secretion of mucus. They possess a peculiar "astringent" *taste.*

The manner in which this astringent action is brought about is still only imperfectly understood. All astringents produce precipitation of proteids, and this insoluble proteid precipitate seems to underlie the astringent action. The principal drugs which produce such a precipitate are the metallic salts, vegetable tannins, substances like alcohol, and dilute acids. To explain this action it has been assumed that these precipitates form a lining along the capillary walls, and in this way add an additional coat, as it were, to each capillary. It seems, however, much more likely that they act by coagulating the ordinarily semifluid cement substance between the endothelial cells, and that this prevents the filtration of fluids, and more especially the emigration of cells. The *absorption of already formed effusions*, to which they lead, may possibly be explained by osmotic laws: By precipitating the proteids of these effusions, they lower their molecular concentration, and render them more diffusible.

Not all proteid precipitants are astringents. The precipitant action must be of a special kind. It must be produced very quickly, and the precipitate must be practically impermeable to the precipitant. Otherwise the precipitant action would extend so deeply as to lead to extensive necrosis, and would thus continue the inflammatory process. We repeat, that the main essential to astringency is that the precipitate will prevent further penetration of the astringent into healthy tissues. Its action must be confined to the inflamed area—to the place where it is applied. From this it follows that it is absolutely *irrational to expect a remote action from astringents.* The very facts of their action exclude such a possibility. Before this was well understood it was tried to obtain astringent action throughout the body by external application or by giving astringents by the mouth. The want of success confirmed what has just been said.

In the *intestinal canal* the astringents seem to form a deposit along the lumen of the intestine, and in this way prevent absorption, and also the penetration of other irritant substances, in this way lessening peristalsis.

III. GENERAL TOXICOLOGY OF IRRITANTS.

The phenomena produced by irritant poisons will, of course, depend in the first place upon the part of the body with which they are brought into immediate contact. The most prominent symptoms arise from the skin, alimentary canal, or respiratory organs; the last only in the case of very volatile poisons. Later symptoms may appear in the urinary organs.

The extent of the action depends upon the concentration of the poisons, the time during which they act, and the extent of surface with which they come into contact—less upon their absolute amount. If taken by the alimentary canal, their action will also be modified by the presence of food.

1. Cauterization of the Skin.—This may be either accidental or criminal. In the latter case it is usually by sulphuric acid ("Vitriol"). The *results* are the same as in the case of extensive burns. The *diagnosis* offers no difficulty. The character of the stains is that described on page 659. Sufficient of the corrosive can always be collected from the clothing, etc., to establish its identity by chemic means. The *treatment* is precisely like that for burns, after previous neutralization and removal of the corrosive agent. Salves and oils are useful—especially the Linimentum Calcis (Carron Oil, *i. e.*, equal parts Linseed Oil and Lime-water).

2. **Poisoning by the Alimentary Canal.**—The introduction of caustics by the mouth is almost always either accidental or suicidal. The effects are so painful and appear so promptly, and the lesions are so persistent, that they would scarcely ever be used in criminal poisoning—except possibly in infanticide. They are sometimes taken by mistake for syrup or other medicine, and may be swallowed before the difference is noticed. However, certain organic irritants, usually insoluble, such as croton oil, do not produce their action for some time.

The phenomena vary according to whether the irritant produces an actual cauterization—a destruction or solution of the tissues; or whether it causes only inflammation. We shall begin with the latter class.

(A) **Irritants which do not destroy the tissue:** To this class belong elaterium, croton oil, and most of the other organic irritants, such as volatile oils, etc.

The symptoms are those of a violent **gastro-enteritis:** nausea, vomiting, and diarrhea. If the poison will act only when dissolved, and is insoluble in the stomach, as is croton oil, the nausea and vomiting will not be present, but only the diarrhea. The symptoms will appear correspondingly late. The abdomen is usually distended and extremely painful, especially upon pressure. As a result of the gastro-enteritis, there will be an extensive dilatation of the splanchnic area, and consequently withdrawal of blood from other parts of the body. This will produce marked changes in the circulation. The pulse will be soft, small, and quick. The *lowered circulation* will react upon other organs, and most conspicuously upon the *central nervous system.* There is great anxiety, vertigo, delirium, convulsions, then *collapse*, and finally coma and death. This picture is common to the entire series of irritant poisons.

Abortion.—The hyperemia is not confined to the intestine, but extends to all the abdominal organs, which therefore partake in the inflammation, although they do not come into direct contact with the irritant. The most important organ involved in this is the uterus, and the organic irritants have been very frequently used to procure criminal abortion. Oil of savin, of tansy, and of pennyroyal enjoy a special reputation in this connection, but any other irritant produces the same result. The ecbolic effect is only secondary to the gastro-enteritis, and the latter is very often fatal without accomplishing the object for which it was produced.

The *postmortem appearances* are those of gastro-enteritis, and in cases of suspected criminal abortion this must be of sufficient extent to explain the fatal issue. The pathologic condition consists in an intense congestion of the entire contents of the alimentary canal, often with inflammatory exudate into the lumen of the intestine. The congestion may be so violent as to produce ecchymoses. If these are present, the vomit and stools will be tinged with blood during life. Destruction of tissue is quite rare. It may, however, occur from gangrene due to the interference with the circulation.

(B) **The fixed caustics:** The poisons which are of greatest importance in this connection are the mineral acids, and, to a much less extent, carbolic acid; oxalic acid, which, however, stands apart on account of its specific toxic action; the organic acids, which are, generally speaking, corrosive in proportion to their volatility; the alkalies, the alkaline earths, and the carbonates; the haloid substances, bromin, chlorin, and iodin. Metals are also to some extent corrosive, but not usually sufficiently so to produce perforation. The alkalies and bromin produce the most extensive destruction of tissue, because of their deep penetration. With them, the scar-formation is also the most extensive.

All caustics will cause symptoms from the destruction of the tissues with which they come into contact, in addition to the gastro-enteritis. The importance of this lies in the reflex affection of the central nervous system—in **shock**—which may appear so quickly and be so violent as to entirely cover up the local symptoms. Death may occur before vomiting and diarrhea have had time to develop.

A further importance of the corrosive action lies in the fact that it may produce perforation, and consequently peritonitis, and death from this cause. If the poisoning is not immediately fatal, the corrosion will lead to scar-formation, and consequently stenosis, and the patient very frequently dies after a long time from inanition due to the interference of the stenosis with swallowing, etc.

The *acute symptoms* begin in the mouth, with a burning pain, dysphagia, and loss of tissue.

The taste of many of these substances is characteristic—acid, alkaline, metallic, astringent, etc. The nature of the corrosion in the mouth is of great diagnostic importance.

Alkalies cause a transparent swelling of the epithelium, which will detach as a gelatinous mass, exposing the scarlet-colored inflamed area beneath. The other corrosives, which precipitate proteids, produce at first a grayish-white opaque stain. This persists in the case of the metallic poisons. The acids, however, change the hemoglobin in the neighboring area into the dark acid-hematin, and the color of the stain consequently becomes dark or black. Nitric acid is an exception: its stain takes on a yellow color. This differs from that of picric acid by being changed to orange by alkalies, whilst the picric acid stain remains unaltered. Bromin produces a characteristic light brown or orange stain; iodin stains a mahogany color. The silver stain turns black after a time.[1]

The *esophagus* is also corroded, and ordinarily especially at its beginning and end, and at the place where it crosses the left bronchus.

In the *stomach* the principal corrosions will be found at the pylorus, since the caustic follows the lesser curvature and accumulates at the pyloric end.

The symptoms consist in the gastro-enteritis which has been described. The vomiting and diarrhea are more frequently bloody. In the case of acids the vomited blood is frequently very dark in color on account of the formation of acid hematin. This is the so-called "coffee-grounds" vomit. The pain is very much more marked with corrosive poisons. Death from gastro-enteritis may ensue in from twenty-four to forty-eight hours. The absorption of the products of the chemic action of these agents on the tissues very frequently leads to fever. On the other hand, the collapse may lead to a fall of temperature.

In the *postmortem examination* one would look for evidence of destruction of tissue in the gastro-intestinal canal. This would be found in the upper portions in the case of most of the ordinary corrosive poisons, as acids, alkalies, and haloids; whereas with metals it is often in the cecum or large intestine, because they are excreted in these situations.

When the action has not progressed to actual corrosion, there is often very marked hyperemia and ecchymosis. The color is frequently much darker than corresponds to the amount of congestion, especially in the case of acids (due to acid hematin). Alkalies, on the other hand, have a tendency to make the blood appear lighter.

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[1] The stains of iodin and silver are frequently a source of annoyance in the therapeutic exhibition of these. They can be readily removed: The Iodin by ammonia water; the silver by potassium cyanid, or by painting first with iodin and then with ammonia.

The other abdominal organs are also hyperemic.

3. Volatile Caustics.—

These comprise ammonia, chlorin, bromin, the fuming mineral acids, the gaseous acids, such as sulphurous, nitrous, etc.; and certain organic acids—acetic, formic, etc. Also other organic substances, such as formaldehyd; and the volatile oils, especially the oil of mustard.

These show effects upon the respiratory organs, in addition to the symptoms already described. They also affect the central nervous system more profoundly, and primarily in the way of a stimulation.

The action upon the respiratory organs may lead to spasm or edema of the glottis, and this may produce death; or, in less degree, permanent or temporary loss of voice, edema of the lungs, bronchitis, bloody sputum, etc. There is usually a reflex stoppage of respiration. This is a conservative measure, and explains why poisoning by these agents is not more fatal. The volatile poisons also affect all other exposed mucous membranes and produce conjunctivitis, coryza, etc.

4. Treatment of Poisoning by Corrosives.—The first measure is *dilution*, since the action is proportional to the concentration. The drinking of water in abundance and the washing out of the stomach are therefore important. If corrosion is already advanced, it is not advisable to pass the stomach-tube. The further treatment consists in the administration of *demulcent* substances, as mucilage or boiled starch; or proteids, as white of egg; or milk. The proteids are especially useful against the metallic poisons, since they form rather insoluble albuminates.

The pain usually requires the exhibition of *narcotics* in free doses. Most of the irritant poisons can be treated by *chemic antidotes;* in the case of alkalies, by acids; in the case of acids and the haloids, by means of alkalies.

For poisoning by acids or haloids the free alkalies are usually too strong. The carbonates, on the other hand, will develop carbonic acid, and this produces distention of the stomach, and therefore pressure on the already weakened organs, and may even lead to rupture. The carbonates are consequently contraindicated. The potassium preparations in general must be avoided, because, in the corroded condition of the stomach, they would probably be absorbed in sufficient amount to produce potassium poisoning. So the choice is practically restricted to soap or magnesium oxid. Of course, in case of necessity one takes almost anything at hand, such as whitewash or chalk; but magnesium oxid should be preferred. In the case of alkali-poisoning any dilute acid will do, in strength of about 5%. Vinegar will usually be the most handy, but the nature of the acid is immaterial. Poisoning by bromin or iodin is treated with sodium bicarbonate. Caustics in the eye are best washed away by a free supply of water.

(B) DETAILS OF THE DIFFERENT CLASSES OF IRRITANTS.

After this general survey of the subject of chemic irritation, the different classes may be studied with more detail.

Irritants may be divided into the following groups :

Water and neutral salts of alkalies.
Alkalies ; Sulphur compounds.
Acids ; Haloids.
Metallic salts.
Tannins.
Volatile organic substances.
Mechanical.
Fixed organic substances (cathartics).

1. THE ACTION OF WATER AND THE NEUTRAL SALTS

has been described in Chapter XXIV,. A. It is a pure physical salt action, leading to mild superficial irritation—mild hyperemia and sensory stimulation., With *water* the action on the intact skin is very small indeed, because the stratum corneum prevents penetration. On denuded surfaces, where the stratum corneum has been removed, the action is considerably stronger. It leads here to the death of the superficial cells, and stimulation of the underlying layers to more rapid multiplication. The action on the stomach and intestine is precisely similar. The latter help to explain some of the beneficial effects of "water-cures" in certain cases of dyspepsia. The action on the skin may be obtained by poultices, compresses, or protracted baths, and may conceivably be of use in some skin diseases. But, as has been said, the action is slight; the effects of poultices and baths are almost exclusively thermal and reflex.

Solutions of *neutral salts* stimulate the skin in a similar manner, but somewhat more profoundly. They penetrate more readily, and consequently produce some stimulation on the intact skin. This is quite superficial, but in the shape of sea-water baths it can be made quite extensive, so that salts are especially useful when it is wished to obtain a mild but extensive stimulation of the skin. These salts possess an advantage over most other irritants in that they do not injure the epidermis.

The action of the salts on the stomach and intestine, on the other hand, is rather deep. They are absorbed before they have time to become isotonic, and therefore exert their salt action on all the cells with which they come into contact. They also produce a mild irritation of the renal epithelium. The therapeutic uses of these salts in dyspepsia and as diuretics, as well as their toxicologic importance, and the specific irritant properties of nitrates, chlorates, etc., have been discussed in Chapters XXIV and XXV.

2. ALKALIES.

The group of alkalies includes the free alkalies and those salts which show an alkaline reaction: The carbonates and bicarbonates, borates, sulphids, alkaline cyanids, and basic phosphates.

One must differentiate very sharply between dilute and concentrated solutions.

(a) Dilute solutions cause a stimulation of the cells. They soften the epidermis and emulsify and dissolve fat. On the mucous membranes they effect solution of mucus.

Their use in *cleansing the skin* depends upon the emulsification of fat through the formation of soaps, and upon the softening of the epidermis, so that it is readily removed together with the adhering impurities. In the *mouth* the alkalies have a characteristic soapy taste. In the *stomach* the irritant action may be employed to produce some stimulation, and they aid in the solution of mucus. On the other hand, they may derange digestion by neutralizing the gastric juice. Their action is not very deep, since they are neutralized before they can penetrate.

Their irritant action on the *skin* is employed when a stimulation of extensive areas, together with a softening of the epidermis, is desired; as, for instance, in case of ichthyosis. They are then used in the form of alkaline baths.

Any of the alkaline salts can be used; such as sodium carbonate or bicarbonate, potassium carbonate, or borax, in the proportion of about 100 Gm. per bath; for lotions, 2%. These baths are best administered at night, before going to bed.

(b) Stronger solutions and solid alkalies combine with the tissue elements to form alkaline albuminates, or with the fats to form soaps, and in this way produce a destruction of substance. This determines their use as *caustics*. They are also very hygroscopic, and withdraw water from the cells, which contributes to the necrosis. The scab which they produce is very soft, and the compounds which they form are very soluble; consequently the alkalies penetrate very deeply, and it is difficult to circumscribe their action. This is remedied to some extent by mixing them with insoluble powders. A combination of potash and lime makes a fairly useful preparation. But alkaline caustics are quite painful, and lead to extensive scar-formation, so that they are not popular. Only the free alkalies can be used as caustics, since the carbonates are not sufficiently powerful.

(c) **Ammonia** differs from the other alkalies in penetrating deeper, on account of its greater volatility. It passes through the stratum corneum of the epidermis without injuring it, and, acting upon the lower layers of the skin, produces blisters. It is sometimes used for this purpose instead of cantharides, especially in nephritis, where the latter cannot be employed. It is, however, more painful.

It is frequently used in more dilute form as liniment for counterirritation, when a deep action is desired. Its use as a reflex nervous stimulant has been sufficiently discussed. (See p. 557.)

3. THE SULPHUR COMPOUNDS.

The group of sulphur compounds comprises ***sulphur***, ***sulphuretted hydrogen***, the *sulphids* and *polysulphids*. *Ichthyol* and *Thiol* (see p. 384) can probably be counted to some extent in the same group.

Locally these act as *mild irritants*. H_2S behaves rather like acids. The sulphids and polysulphids are readily decomposed into H_2S and the alkali, so that they exhibit both actions.

Free sulphur does not act at all until it is brought into solution as a sulphid. On the skin this is accomplished through the cutaneous secretions; the more quickly, if the sulphur is applied in moist form or in ointments. In the intestines the change is effected by the sodium carbonate.

Besides this stimulant irritant effect, sulphur also has a mild *antiseptic* and *parasiticidal action*.

In the case of the *skin*, the sulphids produce a softening of the stratum corneum, very much like the alkalies, and they are used in the same conditions. Their action on hair is even greater, so that they are valuable as depilatories, especially calcium sulphid.

Since free sulphur will act only in the measure in which it is converted into sulphids—necessarily a rather slow process—the irritation produced by it will be mild and prolonged. This is the secret of its success.

This holds true not only of the skin, but also of the *intestine*, where the solution is effected principally by the sodium carbonate. Since the amount of this is limited, the strength of the cathartic action will be practically independent of the amount of sulphur administered, except in so far as it serves as a mechanical irritant by its bulk, just as any other insoluble substance. The cathartic action of sulphur is therefore mild and limited to a softening of the stools, without rendering them fluid. This is of especial value in cases in which a softening without irritation or active catharsis is indicated, as in hemorrhoids.

The flowers of sulphur are more useful than the precipitated sulphur. The latter is so fine a powder that its conversion into the sulphid may take place too rapidly and produce a stronger action than is desired.

Useful forms for administration are:

Pulv. Glycyrrhizæ Comp.; or Sulphuris and Pot. Bitart., part æq.

Sulphur compounds are very frequently used as *parasiticides* in skin diseases,—itch, etc.,—either in the form of sulphur ointment or sulphur baths. For the latter, sulphurated potash, 30 to 200 Gm. (2 to 6 ozs.) per bath.

The sulphids are oxidized in the body, and excreted as sulphates. This occurs so rapidly that they never produce their systemic ion action when given by the mouth.

If *injected directly into the circulation*, they, as well as sulphuretted hydrogen, produce a stimulation and then depression of the central nervous system. Their irritant action may also be exerted on the respiratory passages, because sulphuretted hydrogen is excreted to some extent by this channel. They have therefore been given as expectorants, but do not seem to be very efficient.

Sulphur, especially in the form of *sulphur spring-water*, has been recommended for a variety of obscure diseases—rheumatism, gout, diabetes, etc. It is doubtful whether the benefits are due to the sulphur, for the amount of this is very small. As far as they have any effects, they would be mildly laxative. The benefits must rather be attributed to the other hygienic measures, especially when they are used in the form of baths.

The sulphids have been proposed as an *antidote for hydrocyanic acid*, since they would form sulphocyanids, which do not have the hydrocyanic acid action. This has not been tested. It is possible that the reaction goes on too slowly to be of value.

MATERIA MEDICA OF SULPHUR COMPOUNDS.

Sulphur Sublimatum (U.S.P., B.P.).—(*Flowers of Sulphur.*)—S. The sublimed crude sulphur. *Dose:* 1 to 4 Gm. (15 to 60 grains). Insoluble.

⁂ *Sulphur Lotum* (U.S.P.).—*Washed Sulphur.*—Sulphur washed with ammonia water, to remove free acid. *Dose:* same.

Enters into the preparation of:

⁂ *Unguentum Sulphuris* (U.S.P., B.P.).—30%. (Benzoinated Lard.)

⁂ *Pulvis Glycyrrhizæ Compositus* (U.S.P., B.P.).—Contains 8% (10%, B.P.) of sulphur. Dose 4 to 8 Gm. (1 to 2 drachms).

Sulphur Precipitatum (U.S.P., B.P.).—(Lac Sulphuris, Milk of Sulphur.) —Made by precipitating a solution of sulphurated lime with HCl. *Dose:* as above.

Calx Sulphurata (U.S.P., B.P.).—Made by reducing Calcium Sulphate by heating with charcoal. Contains 60% of CaS.

Potassa Sulphurata (U.S.P., B.P.).—(*Liver of Sulphur.*) Made by fusing S and K_2CO_3. Soluble in 2 parts of water.

⁂ *Ichthyol.*—An ammonium sulphonate of an oil obtained by the distillation of a bituminous mineral—rich in fossils—found in Tyrol. Contains 10% of Sulphur. Soluble in water, glycerin, and all kinds of fats. Used in strengths of 5 to 50%. Recommended internally in pulmonary disease (4 Gm. per day).

* *Thiol.*—An artificial substitute, used in the same manner.

4. ACIDS.

(a) **Members.**—The most typical acids in regard to the local action are *sulphuric* and *hydrochloric acid*. *Nitric* acid produces the same effects, but differs from these in its chemic action, producing xanthoproteic acid from the proteids. The *sulphurous acid* has also a marked corrosive power. *Hydrofluoric acid* has a specific toxic action, penetrates very deeply in virtue of its volatility, and is especially strongly corrosive. Of the *organic acids*, those of the fatty series act similarly, but are weaker. The *trichlor-acetic acid* is the most corrosive of these. The volatility of most of the fatty acids makes them more penetrating than the mineral acids. *Oxalic acid* occupies a place by itself on account of its specific toxic action, produced probably by the precipitation of the calcium.

The *compound acids*—such as ethyl-sulphuric, etc.—act like organic acids. The *aromatic acids* act partly as acids, but this action is greatly obscured by their collapse action.

The irritant action of the acids is also shared to some extent by the *acid salts*, acid tartrates, acid sulphates, etc.

(b) The **nature of the caustic action** produced by acids varies to some extent with the constituents of the tissues. But, on the whole, it consists, with concentrated acids, in withdrawal of water; in the formation of acid albumins; in softening of the connective tissue and epithelium; and in special situations, in solution of calcareous material.

All the concentrated acids have an affinity for water, and withdraw this from the cells. This affinity is so strong in the case of concentrated H_2SO_4 that not only the formed water is withdrawn from the tissues, but the elements H and O are split off from their chemic combinations with carbon, leading to carbonization.

All acids convert *proteids* into acid-albumins, which are insoluble in moderately strong, but soluble in concentrated or very weak acids. Upon this precipitation of proteids depends their astringent and styptic action.

* Not official.

The most important preparations are marked ⁂.

The *connective tissue* undergoes a rather peculiar change. It is not dissolved, but is softened and rendered more soluble in boiling water. (This explains why meat becomes more tender on keeping.) The concentrated acids have a similar effect upon *epithelium*. Without actually dissolving it, they soften it in such a manner that it is readily detached. Dilute acids, on the other hand, harden it.

The profound tissue destruction by acids gives rise to extensive scar-formation. For this reason, and because they are very painful, they are not much used as caustics.

The destruction of proteids makes acids efficient antiseptics. Even quite dilute solutions, such as the gastric juice, suffice to limit the growth of bacteria. The concentrated acids destroy them outright.

(c) **Dilute solutions** of acids produce a mild irritation, and at the same time harden the epithelium, without destroying it. They are therefore preferred to alkalies as counterirritants.

They differ from the volatile organic irritants in that they do not penetrate so deeply, and do not cause nephritis. They are therefore specifically indicated in certain conditions.

For this purpose they may be used in the form of baths, in the strength of about 30 c.c. (1 ounce) to the bath (30 gallons). Or they may be applied as lotions. In this case the volatile acids are preferred, because their action is deeper.

Formic acid has a special reputation. It is used in the strength of about 4% or 5% in alcohol.

This stimulation of the skin without destruction of epidermis is very frequently used to increase the amount of sweat; and acids, usually in the form of vinegar, are therefore used for sponging in fever. On this account they have received the name of "refrigerants." On the other hand, they are used in excessive secretion of sweat (sweating feet) to harden the epidermis. For this purpose 5 or 10 c.c. of concentrated hydrochloric acid are put in a basin of water and the feet placed in this until they become painful. This is done about twice a week.

Their use in dyspepsia has already been noted on page 581. The continued use of even quite dilute solutions of mineral acids (mineral lemonade) leads to chronic gastritis. The irritant action on the alimentary canal is employed to produce catharsis. It has been pointed out (Chap. XXVI) that the free acids will not *reach the intestine*, so that acid salts or acid fruits are used for this purpose.

The irritant action of the volatile acids is sometimes employed to produce reflex stimulation of the central nervous system by inhaling vinegar, etc.

(d) **Continued exposure to the vapors of acids,** as occurs in certain trades, gives rise to chronic bronchitis. They also attack the teeth, and from these the necrosis may spread to the jaw, as with phosphorus. (See p. 649.)

5. THE HALOIDS.

(a) **General.**—These comprise *bromin*, *iodin*, *chlorin*, and the *hypochlorites*.

Their corrosive action is determined by their entering very easily into chemic combinations with all kinds of organic substances, taking from them hydrogen and forming hydrobromic, hydrochloric, and hydriodic acids, which have the ordinary acid actions. If water is present they will set free oxygen in the form of ozone, by combining with the hydrogen of the water; this is also a strong irritant.

(b) **Bromin and Chlorin.**—*Bromin* is the most active of the haloids, because it is at once volatile and fluid. It produces very deep and very extensive destruction of substance, somewhat like the alkalies.

As volatile poisons, *bromin* and *chlorin* have a very strong action upon the respiratory organs. One part in a million of bromin is already disagreeable; 10 : 1,000,000 is said to be dangerous.

The action of bromin and chlorin is purely local.

It has been claimed that they are absorbed and excreted in the free state in the urine. The absurdity of this is shown by the fact that these are used as tests for urea.

Bromin, chlorin, and the hypochlorites are sometimes used as antiseptics. (See Chap. XVII, C.) They have practically no other therapeutic uses.

(c) **Iodin.**—The case is quite different with the remaining haloid, *iodin*. Free iodin forms one of the most useful of counterirritants. Just as in the case of the iodids, however, its almost specific action has in it nothing mysterious, but can be explained on easily understood principles. It precipitates proteids and enters into easily dissociated compounds with them. On this account it remains for a long time at the place where it is applied. At the same time, it penetrates on account of its volatility. Its action is therefore at once lasting and penetrating. The action is comparatively mild, and can be easily graduated by successive applications; so that it is possible to reach very strong sensory irritation without causing a deep destruction of tissue.

These actions suffice to explain its **therapeutic** success. It is used mainly for the removal of *inflammatory products:* in *rheumatism*, *tubercular glands* and swellings, *syphilitic* affections, etc. It was at one time used extensively by injection to cause **adhesive inflammation** in cysts of all kinds. This is extremely painful, and sometimes causes local gangrene, or at times enough is absorbed to cause general symptoms: gastritis, arterial spasm, neurotic conditions, etc. If it is used at all for injection, it should be in the form of the compound (aqueous) solution (Lugol's solution) and not of the alcoholic tincture. It has been displaced almost entirely by surgical treatment In its injection in *goiter* it probably acts simply as a counterirritant, and not as do the iodids given internally.

MATERIA MEDICA OF HALOIDS.

Bromum (U.S.P.).—Br. A brown liquid.

* **Chlorum.**—Cl. A green gas.

Aqua Chlori (U.S.P.).—Contains at least 0.4% of Cl (prepared by acting upon MnO_2 with HCl).

⁂ *Calx Chlorata* (U.S.P.) [*Calx Chlorinata*, B.P.]—*Chlorinated Lime.* —(*Bleaching powder.*) Made by passing chlorin over slaked lime. Should contain 35% of chlorin which can be liberated by acids.

Liquor Sodæ Chloratæ (U.S.P., B.P.).—*Labarraque's Solution*, Javelle Water.—Made by decomposing Chlorinated Lime with a solution of Sodium Carbonate. Contains at least 2.6% of Chlorin.

Iodum (U.S.P., B.P.).—*Iodin.*—I. Characteristic scales; very sparingly soluble in water, freely in aqueous solution of KI or in 10 parts of Alcohol.

⁂ *Liquor Iodi Compositus* (U.S.P.) —(*Lugol's Solution.*)—I, 5%; KI, 10%. *Dose:* 0.06 to 0.5 c.c. (1 to 10 minims).

Liquor Iodi Fortis (B.P.).—14% I in KI. Externally.

⁂ *Tinctura Iodi* (U.S.P., 7%) [B.P., 2½%]. *Dose:* 0.06 to 0.3 c.c. (1 to 5 minims), diluted.

Unguentum Iodi (U.S.P., B.P.).—4%.

Sulphuris Iodidum (U.S.P., B P.).—Made by fusing sulphur and iodin. Contains 80% of the latter. Use externally like iodin.

Unguentum Sulphuris Iodidi (B.P.).

* *Iodin Tribromid.*—IBr_3. Recommended in anginoica diphtheritica as spray, in 1 : 300 dilution.

* *Iodin Trichlorid.*—ICl_3. Antiseptic (1 : 1000). Soluble in alcohol and water.

⁂ *Iodoformum.*—CHI_3. Prepared by heating iodin, alcohol, and $KHCO_3$. Sets free up to 95% of iodin slowly in contact with tissues. Insoluble in water, soluble in 52 parts alcohol, freely in oil. *Dose:* 0.05 to 0.2 Gm. (1 to 3 grains).

* Not official.

The most important preparations are marked ⁂.

Unguentum Iodoformi.—10% in Benz. Lard.

* *Iodol.*—C_4I_4NH. Treating pyrrol (C_4H_4NH) with iodin. Odorless iodoform substitute. Contains about same percentage of iodin. Insoluble in water.

6. METALLIC SALTS.

(a) General.—The local action of metallic salts (with the exception of arsenic and antimony) is due to their forming compounds with the tissue elements, which are only soluble under certain conditions. In this way the albuminate, etc., of the metal is formed, and the acid of the metallic salt is set free.

If, for instance, a solution of ferric chlorid is added to egg-albumen, the result is an albuminate of iron, and free hydrochloric acid.

This free acid will exert its own irritant action. So that the local effects of metallic salts rest on two factors: the precipitant action of the metal, and the irritant action of the liberated acid. Both will have an influence upon the total effect. The metal proteid compounds are usually of inconstant composition; *i. e.*, they contain varying amounts of metal and proteids.

By taking precautions, perfectly definite compounds may be formed, but as they are usually applied this is not the case.

Some of these metal albuminates are almost insoluble in water; some are soluble in excess of proteid, especially when neutral salts are present; others are not. This solubility is of practical importance in the local action. If the precipitate is soluble, there is no obstacle to the penetration of the metal, and its action, irritant or caustic, is deep. If, on the other hand, the precipitate is insoluble, as in the case of lead salts, penetration cannot take place; the irritation is confined to the surface, and an astringent action results. The difference between caustic and astringent action is therefore mainly one of penetration. In regard to this, the metals stand in about the following order: The most astringent is lead; then comes aluminium; then iron; then zinc, copper, silver, and tin, which stand about on a level; the most caustic is mercury. As to the liberated acids, the strongest caustic action appears in hydrochloric acid; then comes nitric acid; then sulphuric; then phosphoric; the weakest of all are the organic acids—acetic, citric, and tartaric.

By proper combination, then, between the metals and the acids, one may obtain any grade of action from pure caustic to pure astringent.

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* Not official.

The most typical caustic would be mercuric chlorid, the most typical astringent, lead acetate.

The strength of action will, of course, also depend upon the concentration in which the salt is used, and this is often limited by its solubility.

The chlorid of silver would, theoretically, be a stronger caustic than the nitrate, but since it is not soluble, it cannot act in as strong form.

Quite insoluble metallic salts also act, to some extent, either as astringents or as irritants. This is, in part, due simply to their mechanical action.

Even insoluble powders withdraw water, and in this way have some mechanical irritating action.

But in most cases it is due, to a still greater extent, to a small amount of these insoluble salts going into solution by combination with proteids.

It must not be forgotten that the irritant action, the astringent action, and the caustic action, are merely degrees of the same process. The astringent action always precedes the caustic action; and, consequently, by proper dilution, one may obtain astringent effects from salts which are ordinarily purely caustic.

For instance, silver nitrate can be so graduated in strength as to have a purely astringent action, without any caustic effect whatever.

It is therefore impossible to establish a perfectly definite classification between the metallic salts. An approximation to it is given in the following table:

CLASSIFICATION OF METALLIC SALTS.

Mainly Caustic: All Hg salts; $ZnCl_2$; $SnCl_4$; $SbCl_3$; tartar emetic; $CuSO_4$.

Both Caustic and Astringent: Fe salts; $ZnSO_4$; $ZnAc_2$*; $CuAc_2$; $AgNO_3$; $Pb(NO_3)_2$; PbI_2.

Mainly Astringent: Alum; $PbAc_2$; Pb_2OAc_2; ZnO. Bi-subnitrate; white precipitate.

(b) *The* **caustic action** *of metallic salts:* This was formerly used quite extensively, but it has now been largely abandoned. Most are not sufficiently powerful for this purpose; others, again, are too toxic, being absorbed in sufficient amount to produce poisoning. To the latter class belong arsenic, antimony, and mercury. Zinc chlorid and antimony chlorid (Butter of Antimony) are very active caustics, but rather too diffluent. Their scab is so soft that their action cannot be kept within bounds. In fact, of all the metallic caustics, silver nitrate in the form of sticks (Lunar Caustic), and to a less extent copper sulphate, are alone used to produce a purely caustic action. *Arsenic*, were it not for its toxicity, would be a very useful corrosive. Its action is so slow that it can be very readily limited. It was believed to destroy only pathologic formations, leaving healthy tissue intact. This would be easily understood, from the fact that the former are much less staple. *Silver Nitrate* is also quite easily controlled, since its action may be stopped at once by washing with NaCl, which converts it into AgCl.

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* Ac = Acetate.

(c) **Irritant Action of Metallic Corrosives.**—(a) **On the Intact Skin.**—The changes produced by metals are too profound to admit of their employment over large areas, or for a long time. They are most extensively used for local counterirritation; for instance, to cause the absorption of inflammatory effusions, or in certain skin diseases. In the latter, they may be valuable largely on account of their antiseptic action.

Mercury is the strongest, both as regards the irritant and antiseptic effects. It may be used as solutions of corrosive sublimate 1 : 10,000 to 1 : 1000; or as the black or yellow wash (see p. 637); or in the form of ointments. The strength of action of the official ointments is about as follows:

The most irritant and caustic is *Ung. Hydrargyri Nitratis* (Citrin Ointment). Then comes *Ung. Hydrarg. Ammoniat.; Ung. Hydrarg. Oxidi Flavi; Rubri;* least irritant is the *Unguentum Hydrargyri.*

Of other irritant metallic salts, the *Tartar Emetic* is sometimes used in the form of ointment (5 to 10%) to produce pustular eruptions. It is too painful to be popular.

(b) The use of these irritants on **ulcers** and **mucous membranes** is discussed on page 674; their use as **antiseptics**, in Chapter XVII, C.

(c) **On the Intestinal Canal.**—The first effects of the irritant action in this situation are *nausea* and *vomiting*. This is produced by all soluble metallic salts in large doses. But *Copper* and *Zinc* have a rather specifie action, irritating the nerve endings which give rise to the reflex of vomiting, and thus being evacuated before they have time to produce any injury. The dose is therefore almost immaterial, within quite wide limits. (Very large doses may not be completely evacuated and may then cause fatal gastro-enteritis—40 Gm. of $CuSO_4$ proved fatal on the fourth day.) They are usually given in doses of 1 to 3 Gm., dissolved in a glass of water, and repeated in fifteen to thirty minutes if necessary. The effect is very prompt and is accompanied by very little nausea. They are therefore more useful as pure emetics than they are as nauseants. Alum is also given in the same way in doses of 4 to 8 Gm., but is not as quick. Tartar Emetic was formerly much used for this purpose. It causes a more prolonged nausea and is more depressant. Its indications are consequently more those of an expectorant. It should not be used continuously for fear of chronic poisoning.

Certain irritant metallic salts do not, in therapeutic doses, develop much action until they reach the **intestine.** Here they act as cathartics.

The most useful of these are the salts of mercury. Mercurous chlorid—*calomel*—deserves the preference, since it is entirely insoluble in the stomach and so avoids the gastric irritation which accompanies the action of all soluble metallic salts. Its solution in the intestine is due to its forming albuminates which are soluble in the mixture of carbonates and chlorids of the intestinal juice. This is the reason why calomel is less actively cathartic in sucklings than in adults: the intestinal canal of the former contains much less chlorid.

This solution is a slow process, so that it has not usually progressed very far when the excess is removed by the catharsis. The dose is therefore immaterial within rather wide limits—from 0.005 to 1.0 Gm.; and even much larger doses were popular with the old-style physician. These are, however, entirely superfluous, and may become dangerous should conditions be exceptionally favorable to solution. This may occasionally occur. When larger doses are employed, it is usual to mix them with small amounts of vegetable cathartics to hasten their evacuation. Podophyllin, 0.0007, is useful for this purpose. The Pil. Cathart. Comp. of the U.S.P. contains the calomel in serviceable form.

Mercury was formerly considered to stimulate the flow of bile. The fallacy of this has been discussed on page 634.

However, calomel has an advantage over most other cathartics in being distinctly antiseptic, without interfering with the action of ferments. Salts of other metals have also been used as purgatives; thus sulphuret of antimony (Plummer's Pill, see p. 611). Arsenic has a cathartic action, but presents too great danger of toxic effects from absorption.

(d) **On Kidneys:** A mild degree of the irritant action on the renal epithelium—common to all absorbable metals—leads to a diuresis. This is utilized in practice only in the case of calomel. It sometimes succeeds in cases in which caffein, digitalis, etc., have failed.

For this purpose 2 decigrams are given three times a day for two successive days and then intermitted. It must be cautiously given, otherwise it will not cause diuresis but nephritis. The diuresis will only appear about the third day. If it has not been sufficient, the treatment may be repeated on the fifth day. It should not be repeated more than twice, else there is too great danger of general poisoning, or at least of nephritis.

(d) The Astringent Action of Metallic Salts and of Tannins.—

(A) **Members.**—Of the *metallic salts* the most actively astringent is lead acetate; but this cannot be used internally, nor for any length of time externally, on account of the danger of chronic poisoning. Next in activity comes alum, and especially the burnt alum (alum which has been roasted, so as to deprive it of its water of crystallization, and which therefore acts not only as a metallic astringent, but mechanically by withdrawing water). Next to alum come the soluble zinc salts, the sulphate, the acetate, and the sulphocarbolate. Then, after these, insoluble zinc salts, oxid and carbonate. Of other insoluble metallic salts there are especially those of bismuth and cerium, the subnitrate of bismuth and the oxalate of cerium being most commonly used. Then come the caustic salts in proper dilution. The most important is silver nitrate. Then the iron salts in dilute solution; iron sulphate, about 5%; ferric chlorid, about 3%.

In actual use, these different astringents are frequently combined. Whether this has any advantage is somewhat difficult to say. Better results could perhaps be secured by using only one astringent, since its action could be much more exactly controlled.

The materia medica of the tannins is discussed more fully on page 678.

(B) The **therapeutic value** of astringents consists in lessening of the phenomena of chronic inflammation, especially catarrh of mucous membranes. Since their own action is primarily an irritant one, they are apt to increase acute inflammations, and are not so well adapted to their treatment.

They can also be used on wounds, wherever situated and however produced; whether from trauma or ulceration. They lessen the pain by reducing the congestion and swelling; and where there has been destruction of skin or mucous membrane, they afford a mechanical protection for the underlying tissues by forming an artificial membrane through precipitation of the superficial proteids. They also tend to diminish suppuration by rendering the walls of the blood-vessels less permeable to the inflammatory products. They tend to prevent the further penetration of bacteria, and hinder their development by rendering the culture-ground unsuitable. Many are also directly *antiseptic*. They have the advantage over pure antiseptics in a somewhat quicker effect, since they act not only upon the disease factors, but, in addition, upon the symptoms. Where the two properties do not coexist in the same drug, they may be secured by a proper combination of remedies.

The *antiseptic action* of metallic salts has been sufficiently discussed in Chapter XVII, C. We may repeat here that, whilst all metallic salts are antiseptic, they do not act any more upon living organisms than upon dead proteids; consequently they will be weakened in proportion to the amount of proteid present, and the majority act only in pure cultures. Mercury is the only metal which enjoys a specific toxicity, but even with this, the action is greatly weakened by the presence of foreign matter.

Ferrous Sulphate, which is much used in "disinfecting" privy vaults, is deodorant rather than antiseptic. By combining with both H_2S and NH_3, it does much to destroy disagreeable odors, but without harming the bacteria.

For use on open *wounds*, *ulcers*, *abscesses*, etc., for the astringency and a mild nutritive stimulation leading to repair, silver nitrate is the most useful. Next to this, the soluble zinc salts; then alum. They are used in strengths of from ½% to 5%. The insoluble astringents may be used as dusting-powders, or in the form of ointments—5% to 20%. It must not be forgotten that absorption is fairly free from open surfaces, and calomel, bismuth, lead, etc., must be used with caution. Zinc oxid is quite safe, and is one of the most useful.

The *mucous membranes* which are easily accessible to the local action of astringents are those of the mouth, conjunctiva, nose, genito-urinary tract, and rectum. The same salts as in the case of open wounds can be used, as also tannin. They are employed in somewhat weaker solution, as gargles, washes or injections. The usual strength is from ½ to 1%. For vagina or rectum, double this; in the conjunctiva and nose, perhaps one-fourth of this. The strength, as with all local medication, must be adjusted to the anatomic peculiarities of the surface: It should be very different for the cornea and for the plantar surface of the foot. In the case of the genito-urinary tract, irritation is particularly undesirable. For this reason non-irritant proteid compounds of silver have become popular within recent years—Nargol, Protargol, Argentamin.

Astringents cause actual constriction of the mucous membranes, and may in this way bring about the complete disappearance of small polypi.

In the *alimentary canal* the astringents are useful mainly in lessening the reflexes resulting from inflammation; *i. e.*, the vomiting and diarrhea.

Against *vomiting*, especially when caused by ulceration, the insoluble metallic astringents, especially the bismuth subnitrate and the oxalate of cerium, seem to be the most useful. These act not only in virtue of their astringency, but also somewhat after the manner of inert dusting-powder, affording an artificial protective covering to the walls of the viscus by adhering to them. Silver nitrate is also sometimes used in doses of about 1 centigram (1/6 grain), dissolved in water and given three times a day.

Their action on *diarrhea* is entirely similar. Bismuth is again preferred; silver nitrate is often very useful in the summer diarrhea of infants.

The various vegetable drugs containing *tannin* are also very effective. They have been used for a very long time —at least since the fourth century B. C.

The nature of these tannins has already been discussed on page 21. Whilst they all belong to the aromatic series and present certain chemic characters in common, their similarity is mainly a pharmacologic one, resting on the astringent action. This is connected with a remarkable property of precipitating very many classes of substances—proteids, connective tissue, gelatin, as also many alkaloids and glucosids.

There are, however, minor differences between different tannins, in the firmness and solubility of the eschars which they form. These differences may eventually prove of great therapeutic importance, but have at present been too little worked out to be utilized. When these tannins are intended to act upon the intestine,—that is, against diarrhea,—the pure isolated tannins are not as useful as plant extract. This is because the gums, etc., of the latter protect the tannins against decomposition in the stomach.

ANTIDIARRHŒICA:

i. e., Medicines used to lessen peristalsis. The indications for these are to check diarrhea, in peritonitis, and after abdominal operations.

Diarrhea is due to *inflammatory irritation*, the result of faulty digestion, drugs, or bacteria (except in the case of a few *poisons* which stimulate the nerves or muscles directly).

The *etiology* therefore indicates *treatment* by: (1) Removal of the irritant agent, by purging. (2) Limitation of the production of the irritant agent by antiseptics and by reduction of diet (to starchy food). (3) Neutralization of the agent (in cases of acid formation, by alkalies): Chalk, Calcium phosphate, Lime-water. Charcoal is often very efficient.

The *peristalsis* itself may be *diminished* by:

1. Heat, in the form of hot drinks or hot applications.
2. Demulcents (Starches, Acacia).
3. Astringents.
4. Drugs acting upon nerves: Opium or Belladonna.

The diarrhea often results in considerable *weakening* of the patient, to be counteracted by reflex stimulants, as camphor, alcohols, etc.

The principal *Astringents* which are useful in this connection are:

Vegetable:		Mineral:	
Catechu	Rhatany	Bismuth subnitrate	Aluminum hydrate (1 Gm.).
Kino	Tea	" subgallate	———
Hæmatoxylon	Claret	Zinc Oxid, 0.1	Alum enema, 1%.
Coto	Tannin	Silver Nitrate (Pills), 0.01	

These are frequently usefully combined, as in the:

⁂ *Mistura Contra Diarrhœam* (N.F.).—(Sun Cholera Mixture.)—Equal parts of Tincture of Opium, Capsicum, Rhubarb, Camphor, Peppermint. *Dose*, to one teaspoonful. Or: Tr. Opium, Tr. Catechu, Tr. Rhubarb, Sp. Peppermint, Bismuth subnitrate, etc.

The effect of the *continued administration* of small amounts of tannin has considerable importance, because they are contained in a number of beverages; as tea and certain wines. One must distinguish here between the direct irritant action and the chemic action. The stimulant action may be even favorable, just as in the case of iron. On the other hand, larger quantities prove actually irritant, and very large quantities of pure tannin may lead to gastro-enteritis.

Even small amounts of tannin interfere somewhat with absorption. This is largely due to their precipitating proteids. But these combinations are again decomposed in the alkaline intestine, so that the interference is not large.

On the whole, one may say that the small quantities of tannin ordinarily taken with the food and drink are not injurious.

The tannins are *absorbed* to but a very small amount, which is excreted by the urine. The major part is decomposed before absorption, with the formation of a series of decomposition products, amongst which gallic and pyrogallic acids are especially prominent. Neither of these is astringent, so that the specific action of tannin is a purely local one.

The insolubility of tannin compounds has been utilized in securing a more *prolonged local action of the kations*. It will be remembered that this is one reason for the more lasting local effects of galenics as compared with alkaloids. It has been suggested to prepare such combinations artificially, but these have not yet received an extensive trial.

All the metallic salts, the irritant as well as the astringent, and also the vegetable astringents, act as local **styptics**; *i. e.*, lessen local hemorrhage. They do so mainly by the formation of precipitates which occlude the lumen of the small vessels, just as it is occluded ordinarily by fibrin. (Whilst the majority lessen the formation of fibrin, this is overcome by the precipitation.) Besides this precipitation, they also act by injuring the vessel walls in such a way as to produce thrombosis. This is claimed especially for zinc chlorid.

It is scarcely needful to mention that astringents will act only at the place to which they are applied. It is necessary that they come into actual contact with the bleeding vessels. They cannot act through a large clot of blood, and if such exists, it must first be removed. At one time they were used internally with the idea of producing astringent action in remote places; iron was given by the mouth to produce styptic action in the uterus. This was entirely irrational. Their action cannot even extend beyond the stomach, since they are precipitated or decomposed in the intestine.

The indications for the use of styptics are to lessen bleeding, especially capillary oozing. They are sometimes injected into hemorrhoids, and have even been injected into aneurysms. Their injection into larger vessels is dangerous, as it may produce embolism.

The most useful of the metallic styptics are the iron salts, especially the ferric chlorid and ferric sulphate. The ferric chlorid is used either as the solution, or tincture, quite largely diluted with water. Cotton may be steeped in this, forming "styptic cotton." Next comes alum, especially the burnt alum. Then the tannins in any form.

Besides these, any substance which gives a precipitate with proteids will act as styptics in the same manner; *e. g.*, dilute acids in concentrations which need not be at all caustic (vinegar and lemon juice). Quite a number of purely mechanical measures favor the formation of clot; for instance, ordinary cotton or Pengawahr Djambe (this also contains tannin). Cobwebs also form a popular and very effective measure for producing the same result, but are unfortunately very septic. One may obtain the same effect by fine powders which have a strong attraction for water. In case of emergency powdered or granulated sugar is a good styptic, and at the same time antiseptic. Other styptic measures are position, raising the limb and keeping it quiet so as to reduce the local congestion; local pressure; depression of the vasomotor center by narcotics; direct constriction of the vessels by the application of cold, or by drugs, such as cocain, suprarenal extract, hydrastinin, etc.

Sweating Feet: Besides hygienic treatment, the conditions are met by:

1. Acids (see p. 666).
2. Astringents: Silver nitrate 10%, painted on repeatedly until the skin is destroyed. Other astringents, 1 to 5% solution.
3. Antiseptics: Boric acid (saturated solution).
Potass. Permanganate (1 : 1000).
Salicylic acid 10 : 90 Talcum or Zinc Oxid.

(C) MATERIA MEDICA OF TANNINS.

(For the crude drugs see Table on page 680.)

⁂ *Acidum Tannicum* (U.S.P., B.P.).—(*Tannin, Gallotannic Acid, Digallic Acid.*)—$HC_{14}H_9O_9$. Prepared from nutgalls. Soluble in 1 part water, 1 part glycerin, 0.6 part alcohol. Almost insoluble in ether or chloroform. *Dose:* 0.06 to 1.2 Gm. (1 to 20 grains).

Preparations:

Collodium Stypticum (U.S.P.).—(20%.)
Trochisci Acidi Tannici.—U.S.P., each 0.06 Gm. (= 1 grain) Tannin; B.P., each 0.03 Gm. (= ½ grain) Tannin.
Unguentum Acidi Tannici (U.S.P.).—20% in Benz. Lard.
⁂ *Glyceritum Acidi Tannici* (U.S.P., B.P.).—20%.
Suppositoria Acidi Tannici (B.P.).—Each 0.2 Gm. (3 grains) of Tannin.

**Tannal:*	An insoluble Aluminum Tannate	These pass the stomach with very little decomposition. They are given to adults in *doses* of 1 to 5 Gm.; children, 0.3 to 1 Gm.
**Tannalbin:*	" " Albumin-Tannin Precipitate	
**Tannacol:*	" " Gelatin-Tannin Precipitate	

Acidum Gallicum (U.S.P., B.P.).—Gallic Acid.—$C_6H_2(OH)_3CO_2H$.

* Not official.
The most important preparations are marked ⁂.

Occurs in many plants, usually with tannic acid. Prepared by boiling tannin with dilute acids. It does *not* precipitate alkaloids, albumin, or glue. *Dose:* 0.1 to 0.6 Gm. (2 to 12 grains). Externally as astringent (1%), but acts weaker than tannin. Soluble in 100 parts water, 5 parts alcohol.

Pyrogallol (U.S.P.).—(Pyrogallic Acid.)—$C_6H_3(OH)_3$. Soluble in 1.7 parts water, in 1 part alcohol.

7. THERAPEUTICS OF CAUTERIZATION.

Cauterization—the destruction of tissue—is employed:

(A) For removal of tissue or destruction of substance:

1. In case of poisons—snake-bite, etc.;
2. Removal of pathologic tissue;
3. Depilatory;
4. Cicatricial contraction of hypertrophying mucous membranes (nose, etc.);
5. Nerves (teeth);
6. Indolent granulations.

(B) Counterirritation.

In very many cases the chemic cautery has been replaced by galvano- and thermocautery, which are more prompt and permit a more exact limitation of the cauterized area. On the other hand, the slower effect of chemic caustics is of advantage in permitting a graduation in the strength of the action, or in confining it to certain tissue elements. Pathologic formations, being less staple, are in this way more profoundly altered than normal tissue.

The caustics may be applied in solid form (sticks, or fused at the end of a probe), in paste, or in solution—the first being the most strictly localizable, the last the most diffuse. In the latter case, or when the eschar liquefies, the surrounding tissue should be protected by court-plaster.

TABLE OF MOST IMPORTANT CHEMIC CAUTERIZANTS, AND THEIR USES.[1]

Acidum Nitricum: On glass rod. Warts and local tubercles.
Acidum Chromicum: Fused on probe (4).
Acidum Lacticum: On Cotton. Tuberculosis tissue.
Acidum Trichloraceticum: On Cotton (2). Warts.
Acidum Carbolicum: Destruction of infected tissues.
Potassa: Stick.
Calx: Paste (3).
Potassa cum Calce: Paste.
Soda: Stick.
Argenti Nitras: Stick (4, 6).
Zinci Chloridum: Solution (6).
Cupri Sulphas: Crystal. Ulcers of conjunctiva, larynx, etc.

(*Continued on page 682.*)

[1] Numbers refer to indications in preceding table.

⁂ TABLE OF MOST IMPORTANT VEGETABLE ASTRINGENT DRUGS.

NAME OF DRUG.	NAME OF PLANT.	FAMILY.	HABITAT.	PART OF PLANT USED.	MAIN CONSTITUENTS (*2).	PREPARATIONS.			DOSE:	
						Name.	% (U.S. P.).	Menstruum.	Metric.	Apothecaries'.
Quercus (White Oak)	Qu. alba.	Cupuliferæ	N. America.	Bark.	6 to 11% Quercitannic Acid.					
Galla (Nutgall)	(*1)		Levant.		50 to 60% Tannic Acid; 2 to 3% Gallic Acid.	*Tinctura G.*	20	Alcohol and 10% glycerin.	4 to 8 c.c.	1 to 2 ʒ
						Unguentum G.	20	Benz. Lard.		
Catechu (Cutch)	Acacia Catechu [Uncaria Gambier, B.P.]	Leguminosæ.	India.	Extract prepared from wood.	45% Catechutannic Acid.	*Tinctura C. Comp.*	10	One-half alcohol.	2 to 8 c.c.	½ to 2 ʒ
						Trochisci C.		0.06 Gm. (1 grain).		
Krameria (Rhatany)	Krameria species.	Polygaleæ.	S. America.	Root.	20% Krameriatannic Acid.	*Extractum K.*		Aqueous.	0.3 to 0.6	5 to 10 gr.
						Ext. K. Fluid.		Glycerin and one-half alcohol.	0.3 to 2.0	5 to 30 ♏
						Tinctura K.	20	One-half alcohol.	2 to 3	½ to 2 ʒ
						Trochisci K.				
Kino	Pterocarpus Marsupium.	Leguminosæ.	India.	Inspissated juice.	75% Kinotannic Acid.	*Tinctura K.*	10	Glycerin and alcohol.	1 to 8	¼ to 2 ʒ
Hæmatoxylon (Logwood) . .	Hæmatoxylon Campechianum.	Leguminosæ.	Central America.	Wood.	12% Hæmatoxylin.	*Extractum H.*		Aqueous.	0.3 to 1.0	5 to 15 gr.
Hamamelis (Witch-hazel) .	Hamamelis Virginiana.	Hamamelaceæ.	N. America.	Leaves (collected in autumn).	8% Tannic Acid.	*Ext. H. Fluid.*		Glyc., alc., water.	2 to 8 c.c.	½ to 2 ʒ

Rhus Glabra (Sumach) . . .	Rhus glabra.	Anacardiaceæ.	N. America.	Fruit.	6 to 27% Tannic Acid. Malates.	*Ext. Rhois Glabræ Fluid.*		Glyc., and dil. alc.	1 to 4 c.c.	¼ to 1 ʒ
Geranium (Cranesbill) .	G. maculatum.	Graminaceæ.	N. America.	Rhizome.	12 to 17% Tannic Acid.	*Ext. G. Fluid.*		Glyc., and dil. alc.	1 to 4 c.c.	¼ to 1 ʒ
Rubus (Blackberry)	Rubus species.	Rosaceæ.	N. America.	Bark of Root.	10 to 13% Tannic Acid.	*Ext. R. Fluid.*		Glyc. and alc., and water.	2 to 8 c.c.	½ to 2 ʒ
						Syrupus Rubi.	25		2 to 8 c.c.	½ to 2 ʒ
						**Elixir Rubi Compositum*, N.F.			2 to 8 c.c.	½ to 2 ʒ
Rumex (Yellow Dock) . . . . . Also cathartic.	Rumex species.	Polygonaceæ.	Temperate Zones.	Root.	Tannin, Chrysophanic Acid, Oxalate.	*Ext. R. Fluid.*		One-half alcohol.	1 to 4 c.c.	¼ to 1 ʒ
Eucalypti Gummi (Red Gum)	Eucalyptus species.	Myrtaceæ.	Australia.	Gum.	Kinotannic Acid. Catechin and Pyrocatechin.	*Trochiscus E. G.*		0.06 Gm. (1 grain).	0.12 to 0.6	2 to 10 grs.
****Coto***	(?)		Bolivia.	Bark.	Cotoin. (*3) Resin.				0.06 to 0.6	(1 to 10 grs.)

(*1) An excrescence on leaves of Quercus lusitanica, caused by the punctures and deposited ova of a wasp, Cynips Gallæ tinctoriæ.
(*2) Most of these drugs also contain bitter principles.
(*3) *Cotoin:* glucosid said to be specific in cholera and also to check night-sweats of phthisis. *Dose:* 0.06 to 0.12 Gm. (1 to 2 grains).
* = Unofficial.

The following plants, used in popular herb-medicine, may be counted in this class:

Castanea—Chestnut.
Heuchera—Alum Weed.
Cornus—Dog-wood.
Kalmia—Mountain Laurel.
Vaccinia—Cranberries.
Juglans—Walnut and Butternut.
Ægle Mamelos—Bael Fruit.
Potentilla—Cinquefoil.
Corylus—Hazel.
Viola—Pansy.
Carya—Hickory.

Hydrargyri Bichloridum } Luetic tissue.
Liquor Hydrargyri Nitratis }
Acidum Arsenosum: Dental nerve. (2.5 mg.—$\frac{1}{25}$ grain—in cavity, guarded by cotton.)

8. STRENGTH OF MOST USEFUL SOLUTIONS OF ASTRINGENTS AND ANTISEPTICS.[1]

	Touching Ulcers, Gargles, Rectal and Vaginal Injections.	Urethral Injections and Eye-washes.	Baths (Gm. per Bath, 200 Liters—30 Gal.).	Foot-bath (5 Liters).
Neutral Salts:				
Sodii Chloridum .	1%	0.9%	4 Kg.	
Alkalies:				
Sodii Bicarbon. .	0.2 to 1%	0.2%	100 Gm.	
Sodii Carbonas .			100 Gm.	
Potassii Carbonas			100 Gm.	
Sulphids:				
Pot. sulphurat. .			50 to 150 Gm.	
Acids (Mineral) .	0.5%	0.5%	30 c.c. (1 oz.)	30 to 50 c.c.
Haloids:				
Iodin	0.1 to 1%			
Metallic Salts:				
Zinc Sulphate or Sulphocarbolate	1.5 to 1%	0.2 to 0.4%		
Mercuric Chlorid	0.05 to 0.1%	0.025%		
Liq. Plumbi Subacet. Dil. . .	Full strength.	Full strength.		
Silver nitrate . .	0.5 to 5%	0.2 to 0.5%		
Tr. Ferri Chloridi	10% (of Tr.)			
Alumen and Alum Salts	3%	0.25%		
Cupric Sulphate .	1%	0.5%		
Lead Acetate . .	1%	0.5%		
Tannins:				
Tannic Acid. . .	1 to 3%	0.5 to 2%		
Miscellaneous:				
Boric Acid, or Borax	4% (sat'd)	2% (½ sat'd)		
H_2O_2	¼ to ½ liquor.	⅛ liquor.		
Pot. Permangan.	1 to 2%	0.4%		
Glycerin	20%	10%		
Carbolic Acid . .	1%	0.2%		
Thymol, Essential Oils	Saturated. Watery.	Saturated. Watery.		
Alkaloids:				
Morphin		0.2		
Most Alkaloids for Eye		0.5 to 1%		

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[1] (1% = 5 grains per ounce.) When several are combined, the dose of each must be correspondingly decreased.

Baths: Usually taken in the evening before going to bed. Metal-lined tubs must be avoided for medicated baths.

Gargles: No toxic substance should be used, especially with children, on account of the danger of swallowing. The metallic salts attack the teeth, so that they cannot be employed for a long time.

Urethral Injections: Always have the patient urinate just before injecting, to remove bacteria. Let injection remain at least one minute, then let flow out, but patient should not micturate immediately after.

CHAPTER XXIX.

IRRITANTS (Continued).

9. VOLATILE ORGANIC IRRITANTS.

Any substance which is volatile will penetrate cells in virtue of this property. Not being a normal constituent of protoplasm, it will act as a "molecular foreign body," and cause irritation, just as gross foreign bodies cause irritation when introduced into the organism. Their action may therefore be looked upon as purely physical, and as connected with their volatility.

Many volatile irritants have already been studied, and it is only necessary to review them by name. Their main action is the same as that which will be studied more in detail below.

Volatile Irritants:

1. *Fatty Series:* Alcohol, Ether, Chloroform, Petroleum, etc.
2. *Aromatic Series:* Benzol, Phenol, the Aromatic Acids, etc.
3. *Volatile Acids* (Acetic, Formic, etc.) and *Volatile Alkalies* (Ammonia).
4. "*Organic Volatile Irritants.*"

The *organic volatile irritants* may be divided into two groups:

1. Those acting *only in virtue of their volatility*—represented by Turpentine.
2. Those having a *specific action*—represented by Mustard.

(A) TURPENTINE GROUP (VOLATILE OILS).

1. **General.**—This comprises the great majority of volatile oils, both those which are liquid at ordinary temperature (eleoptenes) and those which are solid (stearoptenes). Examples of the latter are camphor, menthol, and thymol. The chemistry of these oils has been referred to in Chapter XXI, A. They differ only quantitatively in their action. To this group may also be added the balsams and natural resins, since these contain volatile oils.

The action of volatile irritants occurs along the same general lines as with the fixed irritants. They penetrate more readily and have a deeper action. They therefore cause a more profound sensory stimulation for a given amount of caustic action. The latter is very weak or entirely absent with the volatile oils—they cause at most inflammatory necrosis, not chemic corrosion. The sensory stimulation is commonly followed by anesthesia.

Certain of these oils affect nerves in a specific manner; many act as *flavors* (see Chapter VI, B); others (menthol) cause a specific stimulation of the *cold-nerves.*

2. Their action on the olfactory nerves makes them rapid and effective **reflex medullary stimulants,** producing slowing of pulse and rise of blood pressure. Very strong vapors cause respiratory tetanus.

This use of volatile irritants, as compared with strychnin, was discussed on page 194. They are especially useful in *fainting.*

The more serviceable for this purpose are:

Ammonium Carbonate; best as smelling-salt.
Acetic Acid; best as aromatic vinegar.
Ether; best as Spiritus Ætheris.

Any pungent substance will answer in an emergency; the burning of a feather under the nose of the patient is a standard household measure.

3. Substances which produce sneezing (**sternutatoria** or *errhines*) act in a similar manner, but have rather passed out of fashion. They are sometimes also useful as local counterirritants in nasal catarrh.

Amongst these may be mentioned:

Tobacco Snuff.	Soap-bark or other Saponins.
Veratrin 1 : 1000 Starch.	Pepper.
Ipecac.	Euphorbium, etc.

4. Hysteric Sedatives.—Certain of these oils have been found empirically to possess a remarkable action in hysteria. Although we cannot furnish any explanation for their effect, it can scarcely be doubted that it really exists. These substances have for the most part a pronounced odor—disagreeable to most normal individuals, but apparently rather grateful in hysteric conditions. The effect appears to be tied to the odor; valerianic acid is effectual only in proportion as it retains the smell.

The most important of these remedies are:

MATERIA MEDICA OF ANTIHYSTERICS.

Valeriana (U.S.P.) [*Valerianæ Rhizoma*, (B.P.)].—Valerian.—Rhizome and roots of Valeriana officinalis; Valerianaceæ. Europe and Northern Asia; cultivated.

Constituents: ½ to 2% volatile oil. Valerianic and other organic acids; Tannin and Resins.

Preparations:

Extractum Valerianæ Fluidum (U.S.P.).—Three-fourths alcohol, with 5% Ammonia water. *Dose:* 0.6 to 2 c.c. (10 to 30 minims).

Tinctura Valerianæ (U.S.P.).—20%. Three-fourths alcohol. *Dose:* 2 to 8 c.c. (½ to 2 drachms).

⁂ *Tinctura Valerianæ Ammoniata* (U.S.P., B.P.).—20% (with Aromatic Spirits Ammonia). *Dose:* As the Tincture (diluted).

Valerianates.—The *dose* is 0.6 to 1 Gm. (1 to 15 grains).

	SOLUBILITY:	
	IN WATER.	IN ALCOHOL.
⁂ *Ammonii Valerianas* (U.S.P.)	Very soluble.	Very soluble.
**Sodii Valerianas*	Very soluble.	Very soluble.
Ferri Valerianas (U.S.P.) . . .	Insoluble.	Soluble.
Zinci Valerianas (U.S.P., B.P.) .	100 parts.	40 parts.
Quininæ Valerianas (U.S.P.) .	100 parts.	5 parts.
**Acidum Valerianicum*, $H.C_5H_9O_2$	30 parts.	Readily soluble.

Asafœtida (U.S.P., B.P.).—A gum-resin from the root of Ferula fœtida, Umbelliferæ. Turkestan and Afghanistan.

Constituents: 3 to 9% Volatile oil; 20 to 30% Gum; 45 to 70% Resin. (The alcoholic preparations yield turbid mixtures with aqueous liquids.)

Preparations:

Spiritus Ammoniæ Fœtidus (B.P.).—7.5%. *Dose:* 4 c.c. (1 drachm).

Emulsum Asafœtidæ (U.S.P.).—(*Milk of Asafetida. Asafetida Mixture.*) Four parts rubbed with 100 parts water. *Dose:* 15 to 30 c.c. (½ to 1 ounce).

⁂ *Tinctura Asafœtidæ* (U.S.P., B.P.).—20% alcohol. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

⁂ *Pilulæ Asafœtidæ* (U.S.P.).—0.2 Gm. (3 grains). *Dose:* 1 to 4.

Pil. Aloes et Asafœtidæ (U.S.P.).—0.09 Gm. each Aloes and Asafetida.

Pil. Aloes et Asafœtidæ (B.P.).—*Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Sumbul (U.S.P., B.P.).—(*Musk Root.*) The root of Ferula Sumbul, Umbelliferæ.—Central Asia. *Dose:* 0.2 to 0.6 Gm. (3 to 10 grains).

Constituents: Volatile Oil, Resins, Valerianic and other acids.

Tinctura Sumbul (U.S.P., B.P.).—10%. Two-thirds alcohol. *Dose:* 4 to 15 c.c. (1 to 4 drachms).

* Not official.

The most important preparations are marked ⁂.

* **Symplocarpus.**—(*Skunk-cabbage.*) Root of Symplocarpus fœtidus, Armideæ. North America. *Dose:* 0.3 to 1 Gm.

Moschus. See pages 121 and 466.

* **Cataria.**—(*Catnip.*) The herb of the Nepeta Cataria, Labiatæ. North America. Volatile oil. *Dose:* 1 to 4 Gm. (¼ to 1 drachm).

Oleum Erigerontis (U.S.P.).—The volatile oil from the herb Erigeron Canadense (fleabane); Compositæ. North America. *Dose:* 0.3 to 1 c.c. (5 to 15 minims).

5. **The action of essential oils on the skin** is mainly one of sensory irritation. The inflammatory action does not usually exceed the stage of rubefaction. They are therefore especially useful when a strong sensory irritation without destruction is required, as in *chronic rheumatism* (Turpentine), or *muscular strains and inflammatory swellings* (Witch-hazel, Arnica). They form valuable additions to liniments (1 part oil to 10 parts liniment).

6. They, and particularly the balsams, cause a useful stimulation of **wounds, ulcers, and mucous membranes.**

For **ulcers,** Balsam Peru or Copaiba, applied on lint, or Tr. Myrrhæ, eight times diluted.

Of inflammations of mucous membranes, those of the **urethra** are most often treated by these oils. Their use here, however, rests more upon their antiseptic properties, for all members of the group are germicidal. They have an advantage over most other antiseptics, in that they act on the urinary passages even when taken by the mouth. In this way they disinfect the whole course of the urinary tract.

They are for the most part *excreted* combined with glycuronic acid.[1] These combinations retain the antiseptic and irritant properties of the original oils. The oils most commonly used in the treatment of specific urethritis and cystitis are: *Copaiba, Cubebs, Santal-Wood, Matico, Turpentine.*

It has been shown that urine from patients treated with copaiba is fatal to gonococci, and this holds probably for the other oils. None the less, the urine is still a good culture-medium for other bacteria.

Sodium Salicylate or Benzoate is used for the same purpose, as also Uva Ursi. (The last contains a glucosid, arbutin, which is excreted as the antiseptic hydrochinon.)

7. The first place in which these oils will exert their irritant action when taken by the mouth is, of course, in the

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[1] These combinations are very frequently mistaken for sugar, since glycuronic acid gives Fehling's reaction.

* Not official.

alimentary canal, where they will cause a more or less acute **gastro-enteritis.** This interferes to some extent with their therapeutic employment, but it can largely be averted if they are given on a full stomach. The addition of pepsin also seems to diminish this effect.

The gastro-enteritis is also a most prominent symptom in general poisoning. As in the case of other irritant poisoning, it leads to congestion of the abdominal organs, and thus certain members of this group, especially tansy, savin, pennyroyal, and rue, are popularly used as **ecbolics,** frequently with fatal results.

These oils, as well as those of sassafras, rosemary, and thymol, cause fatty degeneration of organs (see p. 646).

8. During the course of their *excretion* they exert their irritant action on the **kidneys and respiratory passages,** leading in strong degrees to nephritis and bronchitis. Milder stages of this action may be useful. The action upon the kidneys especially results in *diuresis,* which is quite frequently utilized. This is one of the reasons why the tea species are more active in this respect than is hot water alone. Juniper in the form of gin also enjoys a considerable reputation. Turpentine has been employed, but it is better given in the form of terpene hydrate ($=$ turpentine $+ 3H_2O$), since the action of the latter can be more exactly controlled, and is more agreeable to the patient.

9. The excretion through the *respiratory organs* may also be at once stimulating and antiseptic. These substances have, therefore, been used in *tuberculosis*, *fibrinous pneumonia, and* as expectorants in *chronic bronchitis.*

Turpentine prevents experimental tuberculosis in dogs, but it has not been shown that it is curative.

Turpentine also diminishes the secretion from the bronchial mucous membranes in a specific manner, and is therefore useful in certain cases of *cough* and in *asthma.* Terpene hydrate is to be preferred.

The value of essential oils (particularly those enumerated as urinary antiseptics) in **chronic inflammations** of all sorts has been abundantly proved by clinical observations and laboratory experiments. They are much less useful in acute inflammatory conditions. Their action is partly explained by their aseptic and irritant qualities. But the fact that they also lessen aseptic inflammations at points remote from the site of their application, *i. e.*, through the blood, shows that there is somewhat specific in their action. They effect this result by lessening the formation of exudates and by hastening their absorption. The explanation probably lies in a chemotaxis, an attraction for leucocytes. In this way they withdraw these cells from the inflamed area into the blood.

10. After their absorption these oils have an effect upon the **central nervous system** related to that of carbolic acid or camphor.

The majority (valerian, fennel, chamomile, eucalyptus, mint, rosemary, turpentine) diminish the reflex excitability, so that large doses will entirely prevent strychnin convulsions in rabbits. The effective doses are, however, entirely too large to make it possible to employ this action in man. It may aid in the lessening of the attacks of pertussis by creosote and turpentine, inhaled with steam.

This depression is preceded by more or less stimulation, the different oils varying greatly in this respect. The habitual use of *absinthe* produces a peculiar irritability of the motor areas related to epilepsy.

If these oils are injected *hypodermically* they produce at first the reflex action, and in a more marked degree than when they are applied to the surface of the skin. Later their systemic, and still later the renal, actions take place.

MATERIA MEDICA OF TURPENTINE GROUP.

Strictly speaking, this group comprises practically all the volatile oils and stearoptenes, and the drugs from which they are derived. Certain of these are, however, used mainly or exclusively for other properties, such as flavoring, as carminatives, as plasters, etc., and will be studied under other headings, and will at most receive mention by title in the present paragraph.

The oils of the Turpentine group are best subdivided according to the indications for which they are most frequently employed.

1. General Cutaneous Counterirritants (Rubefacients).[1]

For this purpose the oils are usually employed as liniments, diluted with 3 to 10 volumes of alcohol or a fatty oil. They are incompatible with water. Taken internally the *dose* is 0.05 to 0.3 c.c. (1 to 5 minims).

⁂ *Oleum Terebinthinæ* (U.S.P., B.P.).—(*Spirits of Turpentine.*) A volatile oil (a mixture of several isomeric hydrocarbons of the formula $C_{10}H_{16}$) obtained by distillation from Turpentine.

Terebinthina (U.S.P.) [*Thus Americanum* (B.P.)], *Turpentine*,[2] is a solid oleoresin, obtained from various pines (Pinus, Coniferæ; United States and other countries). The residue left after the distillation is "Rosin."

Another preparation, *Oleum Terbinthinæ Rectificatum* (U.S.P.), is made by distilling the oil over lime-water.

Turpentine Oil is insoluble in water, soluble in 3 volumes of alcohol, and in all proportions of oils.

It is employed *externally* in liniments.

It is used as a *spray and in vapor* in bronchitis (teaspoonful to tablespoonful for pint of hot water).

It is also sometimes taken internally against respiratory and urinary diseases, but had best be replaced by Terpene.

As *Anthelmintic* it is given in doses of 2 to 15 c.c. (½ to 4 drachms).

Oil of Turpentine undergoes slow changes on exposure to the air, becoming *ozonized*. This is used as an antidote in phosphorus-poisoning (see p. 649).

Preparations:

⁂ *Linimentum Terebinthinæ* (U.S.P.).—Two parts Oil of Turpentine, 1 of Resin Cerate. (B.P., contains Camphor.)

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[1] Coal Oil may also be counted in this group, in regard to its action.

[2] By "Turpentine" is popularly meant the oil, not the oleoresin.

The most important preparations are marked ⁂.

Linimentum Terebinthinæ Aceticum (B.P.).—Contains Camphor and Acetic Acid.

* *Emulsio Olei Terebinthinæ* (N.F.).—1 : 8.

Pix Liquida, see page 389.

Oleum Erigerontis, see page 686.

Oleum Cajuputi (U.S.P.).—From leaves of *Melaleuca Leucadendron*, Myrtaceæ ; East Indian Islands.

Oleum Rosmarini (U.S.P., B.P.).—From leaves of *Rosmarinus officinalis*, Labiatæ ; cultivated in temperate zone.

Arnicæ Flores (U.S.P.).—From *Arnica montana*, Compositæ ; Europe. Contains a volatile oil, small quantities of volatile acids, and an acrid bitter principle. Used externally as

⁂ *Tinctura Arnicæ Florum* (U.S.P.).—20%. One-half alcohol.

Arnicæ Radix (U.S.P., B.P.) is similar to the flowers in composition and action.

⁂ *Tinctura Arnicæ* (B.P.).—5% in three-fourths alcohol.

⁂ *Aqua Hamamelidis Spirituosa* (N.F.) [*Liquor Hamamelidis*, B.P.]. —(Witch-hazel Water, Witch-hazel Extract.) Made by distilling the fresh twigs of *Hamamelis Virginiana* (see p. 680) with 7% alcohol.

2. Used Especially for Stimulation of Ulcers.

These comprise the balsams—mixtures of resins, volatile oils, and aromatic (antiseptic) acids. They are viscous to solid, and are employed as alcoholic solutions. The evaporation leaves a protective and stimulant coating of the balsam.

⁂ *Balsamum Peruvianum* (U.S.P., B.P.).—A thick balsam, obtained from *Toluifera Pereiræ*, Leguminosæ ; Central America. *Dose:* internally, 0.5 to 2 c.c. (10 to 30 minims).

⁂ *Myrrha* (U.S.P., B.P.).—A solid gum-resin obtained from *Commiphora Myrrha*, Burseraceæ ; Africa and Arabia.

⁂ *Tinctura Myrrhæ* (U.S.P., B.P.).—20% in alcohol. Externally, diluted with 5 to 10 volumes of water.

Myrrh is also a carminative, and will be mentioned on page 715.

Styrax (U.S.P., B.P.).—A thick balsam obtained from *Liquidambar orientalis*, Hamamelaceæ ; Asia Minor. *Dose:* internally as the Balsam of Peru.

Benzoinum (U.S.P., B.P.).—A solid balsam obtained from *Styrax Benzoin*, Styraceæ ; Sumatra, etc. Volatile Oil, Benzoic and Cinnamic Acids.

Preparations:

Tinctura Benzoini (U.S.P.).—20% in alcohol.

⁂ *Tinctura Benzoini Composita* (U.S.P., B.P.).—(*Friar's Balsam, Turlington's Balsam.*) (Mainly used internally as carminative and purgative.) Contains Benzoin, Storax, Tolu, and Aloes. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

The original formula was more complicated. It may be found in the National Formulary as

* *Mistura Oleo-Balsamica* (N.F.).—An alcoholic solution of volatile oils and Balsam of Peru.

3. Used Mainly as Cauterizants to Kill the Nerves in Carious Teeth.

Amongst these may be counted the oils of Cloves, Cinnamon, Sassafras, Gaultheria (Creosote), etc.

* Not official.

The most important preparations are marked ⁂.

4. Used Mainly as Reflex Stimulants, through their Odor, or for Sponging the Skin in Fever.

Here belong the various aromatic oils, usually employed in alcoholic solution. The following unofficial mixtures are useful:

* *Acetum Aromaticum* (N.F.);
* *Tinctura Aromatica* (N.F.);
and the following official:
Tinctura Lavandulæ Composita (U.S.P., B.P.).

5. Used Mainly to Stimulate the Bronchial Mucous Membrane, and as Respiratory Antiseptics.

Ol. Terebinthinæ, especially by inhalation. *Pine Bark* is also used.

Terebenum (U.S.P., B.P.).—$C_{10}H_{16}$. A liquid, obtained by acting on Oil of Turpentine with concentrated H_2SO_4 and distilling. Only slightly soluble in water, but dissolved by an equal volume of alcohol. *Dose:* 0.3 to 1.0 c.c. (5 to 15 minims); best given on sugar, or as inhalation.

⁂ *Terpini Hydras* (U.S.P.). — $C_{10}H_{18}(OH)_2 + H_2O$. Colorless crystals made by acting on oil of turpentine with alcohol and nitric acid. Soluble in 250 water, 10 alcohol. *Dose:* 0.1 to 2.0 Gm. (2 to 30 grains). Also sometimes employed as urinary disinfectant.

Eucalyptus (U.S.P.).—The leaves of *Eucalyptus globulus*, Myrtaceæ. Australia; cultivated.

Contains a resin, volatile oil, etc.

Preparations:

Extractum Eucalypti Fluidum (U.S.P.).—Three-fourths alcohol. *Dose:* 2 to 8 c.c. (½ to 2 drachms). Becomes turbid with water.

⁂ *Elixir Eucalypti* (N.F.).—1 : 8. *Dose:* 8 to 15 c.c. (2 to 4 drachms).

The above Eucalyptus preparations are used mainly when the local (carminative) effect on the intestine is desired.

⁂ *Oleum Eucalypti* (U.S.P., B.P.).—The volatile oil. *Dose:* 0.3 to 2.0 c.c. (5 to 30 minims); or for inhalation.

* *Eucalyptol*, one of the constituents of the oil. The *dose* is the same.

Eucalyptus oil is a very active disinfectant, as well as a local irritant.

Oleum Cubebæ is commonly used; see below; so also is *Thymol*, see page 464.

Balsamum Tolutanum (U.S.P., B.P.).—Its preparations are very popular as vehicles in cough mixtures, etc. It is a solid balsam, derived from *Toluifera Balsamum*, Leguminosæ; Venezuela. It is used as:

⁂ *Syrupus Tolutanus* (U.S.P., B.P.).—*Dose:* ad libitum.

Tinctura Tolutana (U.S.P., B.P.).—10%. *Dose:* 2 to 4 c.c. (½ to 1 drachm). With mucilage.

Grindelia (U.S.P.).—The leaves and flowering tops of *Grindelia robusta* and Gr. squariosa, Compositæ; western North America. Contains a volatile oil, a glucosid, and perhaps also an alkaloid.

It is said to relax the muscular coats of the bronchi and diminish the excretion of mucus. It is therefore used in asthma. Its use in ivy-poisoning is mentioned on page 698.

⁂ *Extractum Grindeliæ Fluidum* (U.S.P.).—Made with alcohol; precipitates with water. *Dose:* 1 to 4 c.c. (¼ to 1 drachm).

6. Used Mainly as Urinary Disinfectants.

These are all rather irritant to the stomach, and are usefully administered in capsules.

* Not official.
The most important preparations are marked ⁂.

⁂ *Copaiba* (U.S.P., B.P.).—A liquid natural oleoresin from *Copaiba Langsdorffii* and other species, Leguminosæ. Brazil and Venezuela.

Constituents: Volatile Oil, Resin, Copaivic Acid.

It is not known which of these is most concerned in the action; but it is very likely that they all contribute. For this reason there seems little ground for the following preparations. Copaiba is insoluble in water, but soluble in alcohol or oils. It has an unpleasant taste and odor, and is apt to irritate the stomach. It is therefore best given in capsules, or at least on a full stomach. The *dose* is 1 to 4 c.c. (¼ to 1 drachm).

It may be made into pills with Magnesia (*Massa Copaibæ*).

Preparations:

Oleum Copaibæ (U.S.P., B.P.).—The volatile oil distilled from copaiba.

Resina Copaibæ (U.S.P.).—The residue from this distillation.

The *dose* of either is the same as of the oleoresin.

(Copaiba is not a true balsam, since it does not contain cinnamic or benzoic acid.)

A favorite method of using this drug in gonorrhea is in the form of—

⁂ *Mistura Copaibæ Composita* (N.F.).—(*Lafayette Mixture.*) An emulsion containing as active ingredients ⅛ each of Copaiba and Sweet Spirits of Niter. *Dose:* 4 to 8 c.c.

Cubeba (U.S.P.) [*Cubebæ Fructus*, B.P.].—The unripe fruit of *Piper Cubeba*, Piperaceæ. Java; cultivated.

Contains a volatile oil and resin, the latter containing cubebic acid.

Whilst the oil is the most frequently employed, the oleoresin or fluid extract would be more rational, as the resin is probably also concerned in the action. Cubeb is less irritant than copaiba.

Preparations:

Oleum Cubebæ (U.S.P., B.P.), } 0.3 to 1.2 c.c. (5 to 20 minims); may
⁂ *Oleoresina Cubebæ* (U.S.P.), } be given on sugar or in capsules.

⁂ *Extractum Cubebæ Fluidum* (U.S.P.).—Alcohol; precipitates with water. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Tinctura Cubebæ (U.S.P., B.P.).—20%. *Dose:* 2 to 12 c.c. (½ to 3 drachms).

⁂ *Trochisci Cubebæ* (U.S.P.).—Each contains 0.4 c.c. of the oleoresin. *Dose:* 1 to 6.

⁂ *Oleum Santali* (U.S.P., B.P.).—A volatile oil distilled from the wood of *Santalum album*, Santalaceæ. Southern India. *Dose:* 0.1 to 0.6 c.c. (2 to 10 minims).

Matico (U.S.P.).—The leaves of *Piper angustifolium*, Piperaceæ. Tropical America. Contain a volatile oil, resins, etc.

Preparations:

Extractum Matico Fluidum (U.S.P.). — Three-fourths alcohol; turbid with water. *Dose:* 2 to 8 c.c. (½ to 2 drachms).

Tinctura Matico (U.S.P.).—10%. One-half alcohol. *Dose:* 15 to 30 c.c. (½ to 1 ounce).

7. Used Chiefly as Diuretics.

It must be remembered that these oils produce diuresis through irritation, and that they are therefore contraindicated in inflammatory conditions of the kidneys or urinary passages.

* *Juniperus* (U.S.P.).—*Juniper Berries.*—The fruit of *Juniperus communis*, Coniferæ. Temperate zone. *Active constituent:* A volatile oil, isomeric with Oil of Turpentine.

Used as infusion, corresponding to 4 to 8 Gm.

Oleum Juniperi (U S P, B.P.).—The volatile oil distilled from the above. *Dose:* 0.1 to 0.6 c.c. (2 to 10 minims); usually given as one of the spirits:

* Not official.

The most important preparations are marked ⁂.

Spiritus Juniperi (U.S.P., B.P.).—5%. *Dose:* 2 to 4 c.c.

⁂ *Spiritus Juniperi Compositus* (U.S.P.).—A substitute for Holland Gin. A solution of oil of juniper, caraway, and fennel in 60% alcohol. *Dose:* to 15 c.c. (½ ounce).

Buchu (U.S.P., B.P.).—The leaves of *Barosma betulina* and *B. crenulata*, Rutaceæ; Southern Africa. Contain a volatile oil, a glucosid, a bitter principle, etc. Best given as infusion.

Extractum Buchu Fluidum (U.S.P.).—Alcohol. *Dose:* 1 to 2 c.c. (15 to 30 minims).

⁂ *Infusum Buchu* (B.P.).—5%. *Dose:* 30 to 65 c.c. (1 to 2 ounces).

Tinctura Buchu (B.P.).—20%. Two-thirds alcohol. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

In this place mention may be made of

Guaiacum (U.S.P.) [*Guaiaci Lignum*, B.P.].—The heart-wood of *Guaiacum officinale*, Zygophylleæ; West Indies and other parts of America. Contains 20 to 25% of the Resin.

Guaiaci Resina (U.S.P., B.P.)—(*Gum Guaiac.*) Its chief constituents are a number of resinous acids.

Preparations (made from the wood):

Mistura Guaiaci (B.P.).—*Dose:* 15 to 30 c.c. (½ to 1 oz.).

Tinctura Guaiaci (U.S.P.).—20%. Alcohol.

Tinctura Guaiaci Ammoniata (U.S.P., B.P.).—20%. Made with aromatic spirits of ammonia.

Trochisci Guaiaci Resinæ (B.P.).—Each contains 0.2 Gm. (3 grains). *Dose:* 2 to 4 c.c.

.Guaiac was formerly of repute in rheumatism, syphilis, etc. Any results were probably due to a purgative and diuretic effect. It is now almost obsolete.

A similar drug is

Xanthoxylum (U.S.P.).—*Prickly Ash.*—The bark of *X. americanum* and *X. Clava-Herculis*, Rutaceæ; North America. It contains berberin, and acts as a bitter.

The *fluid extract* is official (U.S.P.). *Dose:* 0.5 to 2 c.c.

8. Acting Particularly on Pelvic Organs.

Certain volatile oils have a strong action on the alimentary canal, producing gastro-enteritis; and through this, hyperemia of the pelvic viscera (see p. 657). This has led to their employment for the procuring of criminal abortion, and they have a toxicologic importance, since they are usually fatal through a gastro-enteritis before they produce the desired result. These drugs are:

Sabina (U.S.P.). — *Savin.* — The tops of *Juniperus Sabina*, Coniferæ. Temperate climates. The active ingredient is the volatile oil.

Extractum Sabinæ Fluidum (U.S.P.).—*Dose:* 0.3 to 1.0 c.c.

Oleum Sabinæ (U.S.P.).—The active volatile oil. *Dose:* 0.06 to 0.3 c.c.

Tanacetum (U.S.P.).—*Tansy.*—The leaves and tops of *Tanacetum vulgare*, Compositæ; Europe and naturalized. *Dose:* 1 to 4 Gm. The active ingredient is the volatile oil.

* *Oleum Rutæ.*—*Oil of Rue.*—From *Ruta graveolens*, Rutaceæ; Europe and cultivated.

Oleum Hedeomæ (U.S.P.).—*Oil of Pennyroyal.* From *Hedeoma pulegioides*, Labiatæ; North America. *Dose:* 0.06 to 0.3 c.c.

(It is the mildest of these agents, and is really more often used as a carminative.)

* Not official.

The most important preparations are marked ⁂.

(B) MUSTARD OIL GROUP.

Mustard oil differs from the other volatile oils in that it produces a markedly greater irritation. The group also includes volatile oils derived from other cruciferous plants —horse-radish, onion, etc. The active principle of mustard is iso-sulpho-cyanid of allyl (CH_5CNS). This does not exist in the seed, but is formed from potassium myronate (sinigrin) in the presence of water under the influence of the ferment myrosin.

These oils are very diffusible, and, therefore, have a very deep action, without producing very profound destruction of the surface. Although they can produce very violent inflammation, the severe grades of action are so difficult to control that they are mainly useful when a mild but deep irritation is desired. The action must be watched very carefully. The oil is developed comparatively slowly, and one must not leave the mustard in contact with the skin until the desired grade of irritation is obtained, but remove it somewhat earlier.

MATERIA MEDICA.

Sinapis Alba (U.S.P., B.P.).—*White Mustard.*—The seed of Brassica alba, Cruciferæ; Europe and Asia. Cultivated.

Sinapis Nigra (U.S.P., B.P.).—*Black Mustard.* The seed of Brassica nigra, Cruciferæ; Europe and Asia. Cultivated.

The above contain 25% of bland fixed oil, gum, etc., the ferment Myrosin, and the white mustard *Sinalbin;* the black, *Sinigrin* (= Potassium Myronate). The latter yields, on the addition of water, the—

Oleum Sinapis Volatile (U.S.P., B.P.).—(Allyl sulpho-cyanid.) This is too irritant to be useful, but may be employed as—

*** *Spiritus Sinapis* (N.F.), 1 : 50; it also enters into the composition of *Linimentum Sinapis* (B.P.) (p. 708).

Mustard is, however, usually employed as the ground seed (mustard flour). The most convenient preparation is—

*** *Charta Sinapis* (U.S.P., B.P.).—*Mustard Plaster.*—Made from black mustard previously exhausted of fixed oil by Benzin, made into a paste with a solution of india-rubber, and spread on paper. This is moistened with *luke-warm* water, and applied a quarter of an hour to one hour. A deeper action may be secured by the *Mustard poultice*, prepared by spreading a paste made with water and equal parts of mustard and flour on linen. Mustard is also used as an addition to hot foot-baths, being first made into a paste with warm water. Its use as emetic has been mentioned on page 328.

Other Cruciferæ contain similar oils, especially—

Armoraciæ Radix (B.P.).—The fresh root of *Cochlearia Armoracia, Horse-radish.*

The onion—*Allium Cepa;* and Garlic—*Allium sativum* (Liliaceæ), contain similar oils; the latter, Allyl sulphid.

Acrolein, the irritant vapors arising when fats are overheated, may also be counted in this group.

The most important preparations are marked ***.

When mustard oil is heated with alcohol and ammonia, it loses its irritant odor and is converted into Allyl sulpho-carbamid, which, under the name of *Thiosinamin*, has been advanced as a cure for lupus. It is to be used in 15% to 20% alcoholic solution, injected subcutaneously.

(C) CANTHARIDIN GROUP.

1. **Members.**—This group comprises a number of fixed organic principles which exercise a specific irritant action upon the skin. It includes a large number of drugs. *Cantharidin* is the most typical member of the group.

Allied to this are probably the poisons of quite a number of other poisonous insects; especially beetles, but probably that of spiders, flies, snakes, and some bacterial toxins belong to the same large group. This subject has not been sufficiently worked out.

Related in its action to cantharidin is *toxicodendrol*, the poison of poison oak or poison ivy. A substance very closely allied to it, if not identical, is *cardol*. The milky juice of the *euphorbia* and the active principle of *capsicum* are also to be counted in this group. The acrid poisons contained in certain fresh plants, especially of the family of Ranunculaceæ, belong here.

Croton oil forms the transition from this group to that of the intestinal irritants.

2. **Manner of Action.**—The principles of this class seem to penetrate the epidermis fairly readily, probably in virtue of their solubility in oils. Their action is then quite violent, but very superficial, producing vesication. They are active, in very small amounts; $\frac{1}{10}$ mg. cantharidin or $\frac{1}{1000}$ mg. toxicodendrol will produce blisters on the human skin in the course of a few hours.

The weaker members of this group, or smaller amounts of the violent, will produce a superficial and very lasting irritant action. In this way they form useful complements to the volatile irritants, which latter produce a comparatively short action, and the two are very usefully combined. Tincture of capsicum is especially valuable for this purpose.

Taken by the stomach, they produce *gastro-enteritis*. A number of this series are quite readily absorbed, and will then exert their irritant action elsewhere, especially upon the organs of excretion. The action upon the *kidneys* results in diuresis; in higher grades in nephritis, in albuminuria, glycosuria, and even in suppression of the urine. Sufficient may be absorbed from a cantharides blister to cause marked irritation of the kidney. The further portions of the urinary passages—bladder and urethra—will also be irritated, and will give rise reflexly to a *constant desire for micturition*, *priapism*, etc. This nephritis is the main factor in death from cantharidal poisoning.

A very curious fact is the peculiar *immunity* of the hedgehog, chicken, and duck to this nephritic action. This is not due to differences in the absorption, nor to destruction of the poison, for the cantharidin is found in the urine, just as it is in susceptible animals. Nor are these animals immune to other nephritic poisons. The immunity to cantharides is also only partial; even a single injection of a large dose causes chronic nephritis. But taking the fatal dose for man (30 mg. by stomach) as the unit, that for the same weight of hedgehog lies about 3000. For the dog and cat it is about 2.5 (1 mg. per kilo); for the rabbit, about 45.

This immunity to the nephritic action does not confer immunity to the local action on the skin. In this respect, the hedgehog is even more susceptible than the rabbit, which latter animal is almost immune to the cutaneous action.

When injected into the circulation, cantharidin affects the *central nervous system* in a manner similar to carbolic acid; *i. e.*, it produces short stimulation, excitement, and increased reflexes, followed by paralytic symptoms, coma, etc.

This central action is not often seen, being obscured by gastro-enteritis or nephritis.

3. Materia Medica.—

Cantharis (U.S.P., B.P.).—*Cantharides.*—*Spanish Flies.*—The dried beetle, *Cantharis vesicatoria;* Insecta, Coleoptera; southern and central Europe.

The chief *constituents* are a volatile and fixed oil, extractives, and Cantharidin (0.4% to 1%); this is soluble in alcohol, ether, etc., and in oils.

The *dose of Cantharis* is 0.03 to 0.06 Gm. (½ to 1 grain).

Preparations:

⁂ *Ceratum Cantharidis* (U.S.P.) [*Emplastrum Cantharidis*, B.P.].—Contains 32%, with fats and turpentine. This, spread as a plaster, constitutes the Fly Plaster. It requires from six to ten hours to raise a blister, according to the thickness of the skin, its content in fat, and probably also individual susceptibility. Since cantharidin is insoluble in water, it is well that the skin be rather greasy, to facilitate its absorption. The plaster adheres very poorly, and must usually be fixed with adhesive plaster. When the blister has appeared, the plaster should be carefully removed without rupturing the vesicle. The latter is then pierced and dressed with an ointment. This prevents further pain, irritation, or infection. By a "flying blister" is meant a series of blisters raised along the course of a nerve by the application of successive plasters. The *Emplastrum Calefaciens* (B.P.) (Warming Plaster) is somewhat weaker.

Collodium Cantharidatum (U.S.P.) [*Collodium Vesicans*, B.P.].—*Cantharidal Collodion.*—60%. May be used instead of the plaster, being applied directly to the skin until it forms a rather thick pellicle.

⁂ *Tinctura Cantharidis* (U.S.P., 5%) [B.P., 1¼%].—Alcohol. May be used as an addition to liniments (in any proportion) or internally, in *dose* of 0.05 to 1 c.c. (1 to 15 minims).

Acetum Cantharidis (B.P.).—10% solution in 50% Acetic Acid.

The most important preparations are marked ⁂.

Liquor Epispasticus (B.P.).—50% solution in Acetic Ether.
Unguentum Cantharidis (B.P.).—10% in Benzoinated Lard.
* *Linimentum Cantharidis* (N.F.).—15% in Turpentine.

Capsicum (U.S.P.) [**Capsici Fructus**, B.P.].—(*Cayenne Pepper.*)—The fruit of *Capsicum fastigiatum* (U.S.P.) [*C. minimum*, B.P.]; Solanaceæ. Cultivated in tropical countries. The main constituents are: *Capsaicin* and volatile oils and resins, but imperfectly known.

Preparations:

Extractum Capsici Fluidum (U.S.P.).—Alcohol. *Dose:* 0.05 to 0.5 c.c. (1 to 8 drops).

⁂ *Tinctura Capsici* (U.S.P., B.P.).—5% Alcohol. *Dose:* 0.3 to 4 c.c. (5 to 60 minims). In liniments, 1 : 8.

Oleoresina Capsici (U.S.P.).—0.015 to 0.05 c.c. (¼ to 1 minim).

Emplastrum Capsici (U.S.P.).

Unguentum Capsici (B.P.).

4. **Therapeutic Uses.**—**Vesication.**—Cantharis is the most useful of the vesicants.

The fresh Ranunculaceæ, mustard, or croton oil, are sometimes used by the laity, but their action is not so easily controlled as that of cantharis.

When the latter is contraindicated,—*e. g.*, in cases of inflammation of the urinary passages,—it is usually replaced by ammonia water or chloroform, which also produce a vesicant action if their evaporation is prevented, as by covering the point of application by a thimble. These are rather more rapid in action, but much more painful than fly blister, and are, therefore, avoided, if possible.

The vesicant action of cantharides develops rather slowly. It usually requires from five to ten hours. It can be somewhat hastened by removing the cantharides plaster after a few hours and applying a hot poultice.

Blisters in general are *contraindicated* in people of feeble condition, since they may then lead to ulceration. When they are employed for counterirritation, they should not be applied directly over the inflamed part, but at some distance from it. They might otherwise render the inflammation more violent.

Cantharis is one of the most useful remedies in the treatment of **baldness.** It is used in the form of tincture, very greatly diluted with alcohol.

The best treatment for alopecia is prophylactic—frequent washing of the scalp with soap and hot water, followed by cold water. When the diseased condition has set in, there is fairly good prognosis if treated early; very poor, if treatment is begun late. If due to syphilis, the mercurials form the best treatment. Ordinary cases are treated by cutaneous irritants or astringents. Besides cantharides, the most useful are: Sulphur, resorcin, chrysarobin, salicylic acid, ammoniated mercury, calomel—all in 5% to 10% ointment or lotion—and alcohol. Pilocarpin is also supposed to stimulate the growth of hair by increasing the circulation of the scalp. If there is an active inflammatory condition, ichthyol or zinc oxid may prove useful.

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* Not official.

The most important preparations are marked ⁂.

Treatment of Impotence.—Very many drugs have been employed for this purpose, but our knowledge concerning them is still very meager. *Cantharis* is one of the most certain, acting through reflex irritation from the urethral mucous membrane. It is, however, quite dangerous, since effective doses are apt to set up considerable nephritis. Many *essential oils* act in the same manner, and are at once less dangerous and less active. Here belong, *e. g.*, *damiana*, *ginseng*, *mint*, *garlic*, etc., and possibly *camphor*.

Strychnin is thought to be effective by raising the tone of the spinal centers.

Phosphorus and *arsenic* enjoy some reputation. If they are effective at all, it must be through improvement in the general condition of the patient.

Alcohol, *morphin*, *cannabis*, and other narcotics act as aphrodisiacs by stimulating the imagination.

The best treatment for impotence consists, of course, in the removal of the cause and improvement in the general health of the patient by appropriate hygiene.

5. Ivy-poisoning.—This is poisoning by several species of the genus rhus: *R. venenata* (Poison Sumach, the most poisonous), *R. Toxicodendron* (Poison Ivy, Poison Oak); Anacardiaceæ. Similar poisoning is produced by certain tropical trees of the same family, as Lithrea caustica, Anacardium, Semecarpus.

Accidental Ivy-poisoning is quite common, since these plants are of frequent occurrence along the roadside, on fences, in swamps, etc.

Only certain individuals seem to be susceptible to the poisoning, while others may handle or masticate all portions of the plant with absolute impunity. The reason for this difference is very obscure, but it may be remembered that certain animals are immune to cantharidis. In susceptible individuals an extremely small amount of the poisonous principle ($\frac{1}{1000}$ mg.) is sufficient to cause a violent dermatitis. In this way the poisoning may be spread by *contagion*; *i. e.*, sufficient may be passed from the clothing or hands of one person to another to cause poisoning. This is, perhaps, the only instance of contagion by a chemic poison.

The toxic principle was long believed to be a volatile acid, but recent investigation has shown that it is neither an acid nor volatile, but a fixed oil (*toxicodendrol*).

The authenticated cases of poisoning at a distance, which would seem to speak for its volatility, can probably be explained by the oil being carried by dust, pollen, etc.

The active principle is the same for all the species. It has a considerable latent period, from one to nine days, usually four to five days. This does not seem to be influenced by the dose. The action consists in a typical dermatitis, passing through all the successive stages, from hyperemia with itching, to vesication and pustulation.

Taken internally, it is an active irritant, exerting its strongest action upon the kidneys.

The toxic principle is destroyed by alkalies. It forms comparatively insoluble compounds with lead. The methods of *treatment*, therefore, consist either in applying to the skin a paste made with an alkali, preferably castile soap, or else a solution of lead acetate, preferably in alcohol, to loosen the oil. Fluid extract of *Grindelia robusta*, diluted with 4 to 8 volumes of water and used as a wash, is frequently useful.

The very worst treatment which can be imagined is the application of vaselin or other ointments, since they dissolve out the toxicodendrol and tend to spread it over a larger surface.

6. ⁂ **Chrysarobinum and Similar Bodies.**—This principle forms 80% of the *Goa powder* (Araroba powder) found in cavities of the tree Andira Araroba, Leguminosæ; Brazil. By oxidation it yields *chrysophanic* acid. Both have a deep and strong local irritant action. They are used as ointments. (Unguentum Chrysarobini 5%, with Lard.)[1]

Pyrogallol, resorcin, and salicylic acid are similar irritants. They are used in skin diseases and as parasiticides.

Pyrogallol (U.S.P.).—(*Pyrogallic Acid.*)—A white powder easily soluble in water or alcohol. The solutions turn brown, especially in the light. Used as 1 to 5% ointment.

⁂ *Resorcinum* (U.S.P.).—Readily soluble in water or alcohol. Used in 10 to 20% solution in glycerin.

Salicylic Acid (U.S.P., B.P.).—Used on the skin in 5 to 10% ointment or solution. For the removal of corns, the—

⁂ *Collodium Salicylatum Compositum* (N.F.) is a good preparation. It contains 11% of the acid, Extract of Cannabis ind., and flexible collodion. It is applied at night and the corn is scraped in the morning.

Unguentum Acidi Salicylici (B.P.).—2% in Paraffin Ointment.

(D) OTHER FORMS OF COUNTERIRRITATION (MAINLY PHYSICAL).

Any agent capable of producing inflammatory reaction may be employed for counterirritation. These remaining forms of irritation are mainly as follows:

1. Bacterial.
2. Friction (Exercise, Massage), Acupuncture, Scarification.

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[1] A 10% ethereal solution of chrysarobin is used in the treatment of *warts*. It is painted on daily, the dead tissue being pared off.

3. Temperature.
4. Electricity.
5. Venesection.

1. Bacterial Counterirritation.—This method is at present practically obsolete. It was formerly accomplished with setons—a string of some fibrous material was carried through a fold of skin and left there to suppurate. More recently, bacterial counterirritation has been employed in the form of artificial streptococcus infection against various tumors.

2. Friction.—This acts partly by producing hyperemia, partly by massage. The benefit derived from liniments is partly due to the friction used in their application.

Exercise and Massage.—Although counterirritation or other reflex stimulation is only in small part responsible for the effects of exercise and massage, those effects bear in some particulars a sufficiently close resemblance to those of counterirritation to excuse their discussion in this place.

The stimulating effect of **exercise** *in health*, and its use for the preservation of this, and for the development of the body, etc., must be left for text-books of physiology and hygiene.

It is applied to diseases mainly in the form of *Swedish movement* and *massage*.

The **Swedish movement** consists in contracting the muscles against resistance furnished by the operator.

Its advantage over ordinary exercise lies in the exactness with which the effort may be regulated and in the possibility of confining the work to particular muscles.

In **massage** the patient is entirely passive, the muscles being treated by the masseur (or masseuse).

The muscles are put into a state of semiflexion and subjected to a manipulation, generally in centripetal direction. The various movements consist in stroking, kneading, friction, percussion, and their modifications, according to the effect which it is intended to produce.

The results depend upon counterirritation, local changes in the circulation and metabolism, reflex effects upon the central nervous system, and the results of exercise in improving the general nutrition.

To produce the reflex results, light stroking or percussion is employed.

Kneading is more efficient to relieve local swellings or edemas. It is easy to convince one's self of the importance of this when one remembers the rapidity with which the swelling from a hypodermic injection may be made to disappear under manipulation. The venous circulation, and especially the lymphatic circulation in muscles, are influenced very largely by the muscular movements, and are in this way greatly increased by exercise, and still more by massage.

A combination of all the movements is used when it is desired to influence the general nutrition of the patient, to supply general exercise, or to prevent atrophy of the muscles in paralysis, or to break up adhesions, etc.

Acupuncture is the process of pushing needles through the skin into the underlying organs. It sets up a certain amount of inflammatory reaction. This method of treatment is much in favor among the Chinese. It is practically obsolete among other civilized peoples.

Scarification is the process of making small incisions with a knife or needles. Irritants, as croton oil, may be rubbed into the resulting wounds, and the action of the drugs will so be considerably increased.

3. Temperature—Hydrotherapy.—

The effects of baths are so largely due to the heat or cold that these may be included under the general heading of Hydrotherapy. The treatment of disease by these means is really a very ancient practice, alternately popular and neglected, and which has undergone a considerable revival in the nineteenth century. It has been developed so extensively as to constitute a special branch of Therapeutics, and its treatise in detail must be left to larger works.

The effects of heat and cold present a certain amount of similarity, both being irritants. They lead to dermatitis of all degrees, from simple temporary hyperemia to corrosion. The results of this counterirritation are mainly nervous, at once sedative and invigorating. They seem to favor digestion, oxidation, and sleep. They increase the excretion of nitrogen (except Russian steam-baths, and, in exceptional cases, tepid salt water baths).

The application of heat acts, of course, as a diaphoretic. (See p. 302.)

(A) General Effects of Cold Baths; *i. e., those having a temperature near or below 70° F.* (21° C.).

These produce at first a contraction of the cutaneous vessels and, in consequence, a sensation of *chilliness*. The *respiration* is reflexly increased and becomes gasping. If the patient is kept in the water, the body-temperature may be somewhat reduced, especially when it is abnormally high. In this case the fall will continue for a little time after the patient has left the bath. As soon as the cold is removed the cutaneous vessels will often dilate very rapidly, bringing an abnormally large amount of blood to the surface. This is usually the case when the skin is vigorously rubbed. The former, the reduction of temperature, determines the usefulness of cold baths in *fever*. The latter, the effect on the cutaneous vessels, acts as a *tonic*. The exercise which this affords to these vessels also serves to harden the body against *exposure*.

When used on persons with feeble circulation, cold baths are apt to do harm rather than good.

Where cold baths are not practicable, they may be replaced by *cold affusions*, *cold sponging*, or by the *cold pack*. In the latter the patient is wrapped in a wet sheet wrung out of cold water, and is then packed in several blankets.

Cold has the same effects when it is restricted to **limited areas.** This may be done either in the form of *compresses* wrung out of cold water or by means of the *ice-bag*. These not only seem to be useful counterirritants, but also appear to *lessen inflammation directly* by producing constriction of the vessels. *Cold foot-baths* are very efficient in checking the menstrual flow. *Cracked ice* taken by the mouth is one of the most efficient means of relieving vomiting. A more intense cold and artificial freezing of the tissues are employed as *local anesthetics* (p. 239).

(B) **Heat** may be applied either dry or moist.

(a) **Heat Bath.—1. Sun Bath.**—The direct rays of the sun produce an active hyperemia of the cutaneous vessels and may lead to dermatitis. Similarly the X-rays, which have found therapeutic application for this purpose.

They produce all grades of dermatitis according to the time during which they are applied and to the susceptibility of the individual.

Sunlight exerts a very conspicuous *tonic effect*. This is indeed in great part psychic; but the oxidizing power is greater in sunlight than in the dark, even in the case of excised tissues.

2. When it is desired to have the action of heat confined to limited areas, this is usually accomplished by *hot-water bags* or **poultices.**

The peculiar advantage of the poultice lies in its applying heat without changing the natural moisture of the skin. The oily basis of the poultice will neither macerate the epidermis nor allow it to lose water. The oil also aids in retaining the heat of the poultice, so that its action extends more deeply than by any other method and with less injury to the superficial layers. A poultice, to be useful, must be very hot, so hot that it needs to be separated from the skin by a few layers of flannel. (For methods of preparing poultices see p. 83.)

3. A somewhat similar result can be attained by wet **compresses** covered by india-rubber or gutta-percha, to prevent evaporation. In this way the body is made to furnish the heat.

4. When the application of dry heat is intended to be more general, it may be used in the form of the **hot-air bath.**

This is one of the most efficient diaphoretic measures. The simplest form of application is to cover the patient with an abundant supply of blankets in a hot room. Other forms are the *Turkish bath*, or the patient may be seated on a chair, enveloped in a blanket, and an alcoholic lamp placed under the seat of the chair.

5. The application of intense heat leads to **cautery.** According to the apparatus used, this is spoken of as *thermocautery* or *galvanocautery*.

A somewhat ancient form of producing a deep but very powerful and painful counterirritation is by placing an ignited *moxa*, a small cone of inflammable material, on the skin.

(b) Moist Heat.—General Warm Baths.

The exact effect of baths will vary with the temperature. *Warm baths* are those with temperatures ranging from 36° to 29° C. (97° to 85° F.). *Hot baths* are above this temperature.

The *warm baths* are used mainly to lessen internal congestion. By dilating the cutaneous vessels they bring more blood to the surface, and so may even reduce the temperature, and may be employed in fevers. By drawing blood from the brain they are useful in insomnia, etc. *Hot baths* may lead to an actual rise in the temperature of the body if they are sufficiently prolonged. They are only used to produce diaphoresis.

Baths may be rendered more specific in their action on the skin by the addition of various medicinal agents, forming **Medicated Baths.** (See p. 683.)

Salt, especially sea salt, in the proportion of 2% to 4%, increases the counterirritation. *Acid* baths are used when a more intense action is desired, with the minimum effect on the epithelium. *Alkaline* and *sulphur* baths are useful in certain skin diseases in which the epithelium is thickened. They are also employed in rheumatism, where their effect must be reflex. General *mustard* baths were formerly used to quicken the appearance of the eruption in exanthemata. They are at present very little employed. They were prepared by adding mustard to water in the proportion of about ½ to 1 teaspoonful to a gallon. The patient is left in this bath only until he feels the first burning in the skin.

Local baths are sometimes employed for the relief of pain or to change the blood supply of a part. This may generally be accomplished more effectually by poultices or hot-water bags. An exception are hot *foot-baths.* These cause a vasomotor dilatation not only in the feet, but also in the whole splanchnic area. They are therefore useful to restore the menstrual flow. They also lessen congestion in the lungs.

The effects of *Russian or steam-baths* are very similar to hot-water baths.

The *Kneip cure*, consisting in walking through wet grass with bare feet, is essentially a cold foot-bath.

4. Electricity.—

The use of electricity in the diagnosis and therapeutics of diseases of the *peripheral nerves* has become so complicated as to be beyond the limits of this treatise. Briefly, the *indications* for its use are to produce irritation or counterirritation, or to prevent muscles from atrophy. The counterirritation is especially valuable in chronic rheumatism. It is employed here in the form of the faradic current. It is also said to be a useful irritant in alopecia, when it is applied in the form of brush electrodes.

5. Venesection, Cupping, and Leeches.[1]—

The effects of these also consist in the change in the distribution of the blood. They are therefore analogous to counterirritation.

It has already been pointed out that the effect of subcutaneous and intravenous *injection of normal salt solutions* is somewhat in the nature of a counterirritation, by chemic stimulation of the vascular endothelium.

(E) RÉSUMÉ OF THERAPEUTICS OF SKIN IRRITANTS.

I. Therapeutic Classification.—These irritants may be divided, according to the extent and manner of their action, into the following classes:

1. Extensive and superficial, without injury to the epidermis: baths, especially salt-water baths.

2. Extensive and superficial, with softening of the epidermis: sulphur and alkali baths.

3. Local, deep, nutritive: iodin, etc.

4. Local, superficial, nutritive: metallic salts, etc.

5. Local, superficial, sensory, brief: volatile oils, turpentine, chloroform, aconite, etc.

6. Local, deep, sensory, lasting: capsicum, caustics (used only in veterinary practice); vesicants: cantharides, ammonia, chloroform.

II. The **indications** for skin irritants may be summarized as follows:

1. In skin diseases.
2. To produce diaphoresis.
3. To reflexly affect the central nervous system, especially the medulla. The volatile irritants are here the most useful.

---

[1] *Leeches* (Hirudo) are applied by holding them to the skin, which has been moistened with milk. They fix themselves, make a peculiar triradiate cut with their mouth, and draw about 5 to 7 c.c. of blood. This quantity may be somewhat increased by applying hot fomentations after removing the animal. Their purpose can usually be better served by cupping.

4. As counterirritants:

(*a*) To change the distribution of the blood and thereby diminish deep chronic inflammation.

(*b*) In a similar manner to remove inflammatory exudates from the connective tissue.

(*c*) To diminish pain.

(*d*) As a tonic to the whole body.

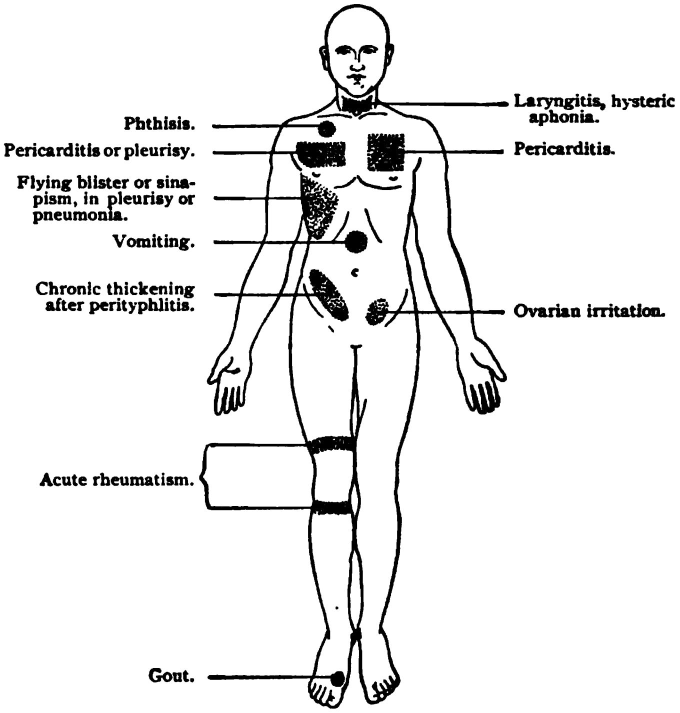
Laryngitis, hysteric aphonia.
Phthisis.
Pericarditis or pleurisy.
Pericarditis.
Flying blister or sinapism, in pleurisy or pneumonia.
Vomiting.
Chronic thickening after perityphlitis.
Ovarian irritation.
Acute rheumatism.
Gout.

Fig. 83.—Diagram of the body showing some of the points where blisters or sinapisms are usually applied. Front view.—(*Brunton.*)

III. Explanatory.—1. For their use in *skin diseases*, see Chapter XXXI, B.

2. For use as *diaphoretics*, see page 303.

3. As reflex irritants of the central nervous system:

To make this subject clear it will suffice to recall the effects of stimulation of the central end of the *sciatic nerve*. A moderate stimulation of this kind produces, reflexly, a slowing of the heart through stimulation of the vagus center; a rise of blood pressure through vasomotor stimulation; and increased respiration through stimulation of the respiratory center. A much stronger stimulation may have precisely the opposite effect; *i. e.*, depress these centers.

The same phenomena result from counterirritants.

Milder degrees of the action are useful in resuscitating patients from *syncope* or from *profound anesthesia.* The quickest action may be obtained either by giving the irritant hypodermically, or by inhaling a volatile irritant, in which case it acts through the trigeminal. One may also employ electricity, or heat or cold applied to the skin.

4. (**a**) and (**b**) **To affect the distribution of blood:** Local changes in the circulation at points remote from the seat of application of the irritant, arise either directly through continuity with the seat of irritation, or through reflexes. By continuity, an increased vascularity of the skin may influence the circulation in neighboring organs in two opposite ways: It either causes hyperemia of the organs simultaneously with its own hyperemia, or it may draw blood

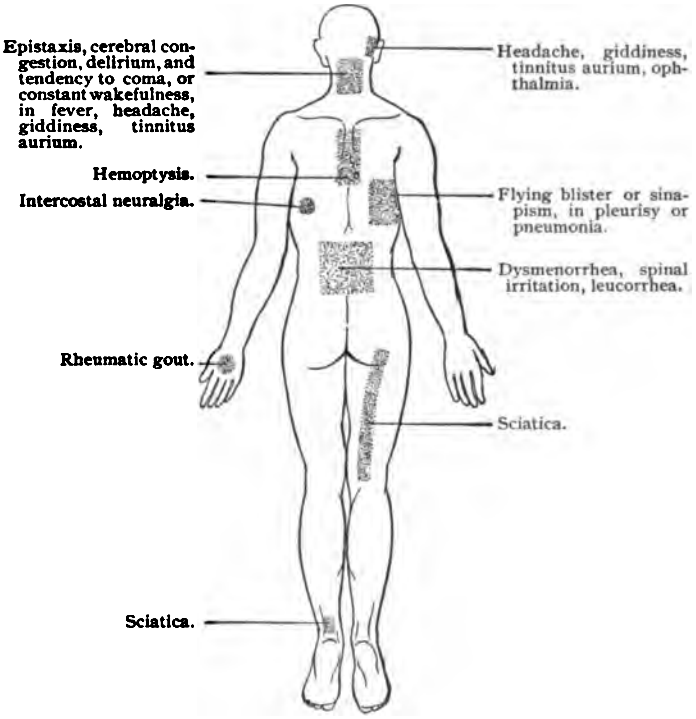
Epistaxis, cerebral congestion, delirium, and tendency to coma, or constant wakefulness, in fever, headache, giddiness, tinnitus aurium.
Headache, giddiness, tinnitus aurium, ophthalmia.
Hemoptysis.
Intercostal neuralgia.
Flying blister or sinapism, in pleurisy or pneumonia.
Dysmenorrhea, spinal irritation, leucorrhea.
Rheumatic gout.
Sciatica.
Sciatica.

Fig. 84.—Diagram of the body showing some of the points where blisters or sinapisms are usually applied. Back view.—(*Brunton.*)

from these organs and thus cause them to become anemic.

We see a hyperemia of this kind in the case of the pelvic organs when the intestinal canal is irritated, whereas this same irritation causes an anemia of the cerebral organs.

Reflexly, changes in the caliber of vessels of cutaneous areas may affect the vascularity of organs at a distance, through the vasomotor centers;

e. g., hot and cold foot-baths will react upon the circulation within the pelvic organs.

To affect the vascularity of the skin, deeply acting and lasting stimulation will be required, as also for the removal of inflammatory products.

4 (c). **To diminish pain:** It has long been known that the application of heat or counterirritants in certain limited superficial situations modifies painful impressions and inflammatory processes in internal organs.

These observations were entirely empirical, but some light has recently been thrown on this subject by the results of Head on the innervation of viscera.

Head comes to the conclusion that the internal organs and definite portions of the surface of the body receive their nerve supply from the same spinal segments, and that irritation of the one will react upon the other. It is remarkable how closely the areas which he mapped out experimentally as corresponding to the internal organs correspond to those positions on which the application of counterirritation has been found empirically most useful (Figs. 83 and 84).

Counterirritation is, as a rule, useful only in chronic inflammation. In acute inflammation there is always a danger of increasing the process or of causing it to extend to neighboring organs.

Liniments: Cutaneous counterirritants are usually employed in the form of liniments; *i. e.*, in solution or suspension in oil. The proportions in which they are used are the following:

Tr. Capsicum	1 : 5.
Tr. Cantharides	
Ammonia Water	
Tr. Belladonna or Opium, etc.	
Spirits Chloroform	
Spirits Ether	
Spirits Camphor	
Tr. Iodin	
Tr. Aconite	1 : 10.
Turpentine	
Sp. Sinapis	
Essential Oils	
Croton Oil	1 : 50.
Creosote	

The Official Liniments are very good representatives of this class of preparations. The composition of the principal ones is as follows:

	U.S.P.		B.P.	
⁂ *Linimentum Ammoniæ:*	Ammonia	35	Ammonia	25
	Alcohol	5	Olive Oil	50
	Water	60	Almond Oil	25
Lin. Belladonnæ:	Camphor	5	F. E. Belladonna	50
	Fl. Ext. Belladonna Root, to	100	Camphor	5
			Alcohol	50
⁂ *Lin. Calcis:* (Carron Oil)	Lime-water, Linseed Oil,	equal parts.	Lime-water, Olive Oil,	equal parts.
⁂ *Lin. Camphoræ:* (Camphorated Oil)	Camphor	20	Camphor	25
	Cotton-seed Oil	80	Cotton-seed Oil	75
⁂ *Lin. Chloroformi:*	Chloroform	30	Chloroform	50
	Soap Liniment	70	Camphor Liniment	50
⁂ *Lin. Saponis:* (Soap Liniment)	Soap	70	Soap	100
	Camphor	45	Camphor	50
	Oil Rosemary	10	Oil Rosemary	20
	Alcohol	750	Alcohol	850
	Water	to 1000	Water	to 1000

This is practically identical with "Opodeldoc."

	U.S.P.		B.P.	
Lin. Saponis Mollis: (Tinctura Saponis Viridis)	Soft Soap	65		
	Oil Lavender	2		
	Alcohol	30		
	Water	to 100		
⁂ *Lin. Sinapis Compositum:*	Mustard Oil	3		
	Fl. Ext. Mezereum	20		
	Camphor	6		
	Castor Oil	15		
	Alcohol	to 100		
Lin. Terebinthinæ:	Resin Cerate	65	Camphor	5
	Oil Turpentine	35	Soft Soap	75
			Water	25
			Oil Turpentine	65

To these may be added the following National Formulary Preparations:

Lin. Aconiti et Chloroformi:	Tr. Aconite	1
	Chloroform	1
	Soap Liniment	6
⁂ *Lin. Cantharidis:*	A 15% solution in oil of turpentine.	
Lin. Iodi:	Iodin	12.5
	KI	5.0
	Glycerin	3.5
	Water	6.5
	Alcohol	to 100.0

Also the B.P. Preparations:

Linimentum Camphoræ Ammoniatum:

Stronger Ammonia	10
Camphor	5
Lavender Oil	¼
Alcohol	to 40

⁂ *Linimentum Aconiti:*

Aconite	60
Alcohol	to 100
Camphor	5

The most important preparations are marked ⁂.

Linimentum Crotonis:

Croton Oil	1.0
Cajeput Oil	3.5
Castor Oil	3.5

⁂ *Linimentum Sinapis:*

Vol. Oil Mustard	2
Camphor	3
Castor Oil	7
Alcohol	43

Linimentum Terebinthinæ Aceticum:

Turpentine	4
Glacial Acetic Acid	1
Camphor Liniment	4

(F) TREATMENT OF ULCERS.

Before leaving the subject of irritants, it may be well to summarize the treatment of *Ulcers* from a pharmacologic standpoint. The following indications may have to be met:

In all cases:
1. To stimulate normal growth and cell division.
2. To form a protective covering against the irritation of the air, etc.
3. To keep the surface aseptic.

In special cases:
4. To destroy unhealthy tissue.
5. To lessen pain.

Several objects may often be obtained by the same drug. Almost every irritant produces secondarily anesthesia. Every irritant which coagulates protoplasm forms a protective covering. Almost every irritant is to some extent antiseptic. But according as one or the other action predominates, the most useful of these drugs may be classified as follows:

1. *Stimulating and forming a rather lasting pellicle of coagulated protoplasm;* mildly antiseptic:

(*a*) The soluble metallic salts, applied with a brush, in 2 to 5% solution; particularly $AgNO_3$ or $ZnSO_4$.

(*b*) The insoluble metallic salts—these also act as absorbents: Zinc oxid; bismuth subnitrate or subgallate; calomel. The last two should only be used on small surfaces. The calomel is also particularly antiseptic; it is usually diluted 5 to 10 times with ZnO. These may be used dry, or in the form of ointments.

2. *Stimulating, but pellicle not lasting:*

$ZnCl_2$, 1%
Alcohol, 20 to 50%
Chloral, 2%
applied with brush.

3. *Producing a lasting stimulation and a resinous protective covering.* Usually incorporated in dressing. Balsams (see p. 689).

4. *Destroying tissue:* $AgNO_3$ stick; $CuSO_4$, 5%.

5. *Antiseptic:* Any of the usual antiseptics may be used for cleansing the surface. But if it is desired to keep it antiseptic, a powder-dressing should be used, such as Iodoform, Aristol, Boric Acid (impalpable powder), Calomel. These also act as absorbents.

(G) PARASITICIDES APPLICABLE TO THE SKIN.

Allied to the cutaneous irritants are the drugs used to destroy parasites infesting the skin. Any antiseptic may be used for this purpose, provided it can be applied in oily

The most important preparations are marked ⁂.

solution. Against bacterial and other vegetable organisms (such as Trichophyton tonsurans) the most popular are the mercury preparations—Unguentum Hydrargyri Ammoniati, or Nitratis. Also sulphur, tar, and the various balsams. All these act, not only by killing the bacteria, but also by causing desquamation, removing the more superficial organisms mechanically, and exposing the deeper-lying parasites to the influence of the drugs.

Of *animal parasites* of the skin, Scabies, the "itch,"—Sarcoptis hominis,—is the most important. It is treated most efficiently with sulphur. Tar, Balsam of Peru, etc., are also used.

Against Pediculi, the best treatment—besides cleanliness—consists probably in Unguentum Hydrargyri. However, Insect Powders (the powdered flowers of species of Pyrethrum—Persian powder—and of Chrysanthemum cinerariæfolium—Dalmatian powder)—are used; also Veratrin and the Sabadilla seeds containing it; Staphisagria; Picrotoxinum. All these are so poisonous, should they be absorbed, that they are not advisable.

CHAPTER XXX.

SPECIFIC IRRITANTS OF THE ALIMENTARY CANAL.

(INCLUDING ANTHELMINTICS.)

It has already been pointed out that certain irritant substances confine their action mainly to the alimentary canal. These are the *Stomachics, Carminatives, and Vegetable Cathartics.*

(A) STOMACHICS.

These may be *defined* as drugs which favorably modify the digestive process in various functional disorders, and whose action rests neither on a chemic nor on a physical basis.

The last portion of the definition excludes ferments, acids and alkalies, and salts.

These substances are characterized by a marked and sharp taste, either *bitter* or "*aromatic.*"

A mixture of the two gives the "*aromatic bitters.*" If the bitters also contain tannin, they are called "*astringent bitters.*"

Manner of Action.—Attempts to verify the action of these stomachics experimentally have not met with success; whereas, clinically, their usefulness is beyond dispute. This need scarcely be considered contradictory. In the experimental investigations, the conditions were almost always those of health, whereas the clinical results have been obtained on cases of disease.

Iron furnishes us another example of a drug which has no action (on hemoglobin formation) in health, but an undoubted effect in disease.

In this dearth of positive experimental results it is impossible to say what constitutes the difference in the action of the two classes—aromatics and bitters. Nor is it possible to predict, even by empirical rules, which will prove the more useful in a given case. However, some difference appears to exist, and they are therefore usefully combined, and indeed their action and taste can both be greatly improved by judicious blending.

What is known about the general actions of these substances furnishes some indication as to the lines along which their specific stomachic action is probably to be explained.

1. Like all substances with a marked taste, they increase reflexly the flow of all digestive fluids, as well as the movements of the stomach. In the bitters this taste is particularly lasting.

2. The aromatics, like other volatile oils, cause an irritation, hyperemia, and increased secretion and motility of the alimentary canal, with consequent improvement in digestion, absorption, *and appetite.* It is likely, but not proven, that bitters also cause an irritation, leading reflexly to the same results. This might be explained by their irritating specifically some nervous end-structures in the stomach, as they do in the tongue.

3. All these substances are more or less antiputrefactive, and tend to lessen the development of bacteria or yeast, and thereby the abnormal fermentations dependent on these.

Small doses of other irritants, such as Ipecac, Rhubarb, and Aloes, also act as stomachics. Very similar results are obtained by alcohol and by the various condiments—salt; acid, as in vinegar; sharp, as in mustard, etc.

The use of these substances dates from the most ancient times, and the "spices of the orient" have played a considerable rôle in the commercial history of the globe. And the bitter substances have held, and still hold, a very prominent place in popular medicine.

Their **uses** may be summarized as follows:

1. To modify or improve the taste of food or medicines; also to obscure a "bad taste in the mouth."

2. To increase digestion in cases of overeating, either in overindulgence in the pleasures of the table, or when it is desired to subject a patient to "forced feeding." In the latter case they act as *tonics.*

3. To increase appetite, from whatever cause this be deficient.

4. To improve digestion in all kinds of "atonic" dyspepsias.

5. As antemetics.

Stomachics are always administered shortly before meals. If there is a catarrhal condition,—*i. e.*, a subacute or chronic inflammation,—the *tannin* of the astringent bitters is apt to be very useful. Ordinarily it is not so. It must be especially avoided when the bitter is to be prescribed with iron, since this makes an unsightly mixture. Tannin-free are the simple bitters (page 712) and the majority of the aromatic bitters (page 714). Pharmacists have attempted to prepare "detannated tinctures," by precipitating the tannin with iron, gelatin, hide, etc. But so far these are not very successful.

In this class of stomachics comes properly a new synthetic compound, **Orexin.** Its tannate is practically tasteless and insoluble, and yet it exerts a very pronounced action in increasing appetite and digestion, somewhat like the group just discussed. It also prevents the distress which follows the eating of certain substances—such as radishes, etc.—in individuals who have an idiosyncrasy against them. *Dose:* 0.1 to 0.4 Gm. (2 to 6 grains) in powders, before meals.

(B) CARMINATIVES.

This class comprises certain aromatic oils exerting an irritant action upon the intestine, being somewhat specific in causing the expulsion of gas rather than of fluid or solid contents. Since they are also antiseptic, they are especially useful in abnormal fermentation, removing at once the discomfort caused by the gas, and checking the growth of the bacteria which gives rise to it. They also form useful additions to laxative mixtures, since they diminish the "griping."

MATERIA MEDICA OF STOMACHICS AND CARMINATIVES.

The number of bitter substances and carminatives is so excessively large that space will permit of the enumeration of only the most important. They will be subdivided as in the text.

I. Simple Bitters

(*i.e.*, practically free from aromatic oils or tannin). Can be mixed with water.

The tinctures have for the most part a strength of 10%.

The *pure alkaloids*, especially

Quinin Sulphate, 0.05 Gm. (1 grain); *Strychnin Sulphate*, 0.001 Gm. ($\frac{1}{60}$ grain); *Berberin sulphate*, 0.1 to 0.3 Gm. (2 to 5 grains).

Calumba (U.S.P., B.P.).—*Colombo.*—The root of *Jateorrhiza palmata*, Menispermaceæ. Eastern Africa; cultivated in East India islands.

Preparations:

Extractum Calumbæ Fluidum (U.S.P.).—*Dose:* 0.3 to 2 c.c. (5 to 30 minims).

Tinctura Calumbæ (U.S.P., B.P.).—10%. *Dose:* 4 to 15 c.c. (1 to 4 drachms).

Infusum Calumbæ (B.P.).—*Dose:* 15 to 30 c.c. (½ to 1 oz.).

Gentiana[1] (U.S.P.).—*Gentian.*—The root of *Gentiana lutea*, Gentianeæ. Switzerland.

Preparations:

Extractum Gentianæ (U.S.P., B.P.).—Used as pill excipient.

Extractum Gentianæ Fluidum (U.S.P.).—*Dose:* 0.3 to 2 c.c. (5 to 30 minims).

⁂ *Tinctura Gentianæ Composita* (U.S.P., B.P.).—10%; with Bitter Orange Peel and Cardamom. *Dose:* 4 to 15 c.c. (1 to 4 drachms).

⁂ *Elixir Gentianæ* (N.F.).—3.5%; detannated by iron. *Dose:* 8 to 30 c.c. (2 to 8 drachms).

Infusum Gentianæ Compositum (B.P.).—Contains Bitter Orange Peel and Lemon Peel. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Quassia (U.S.P., B.P.).—The wood of *Picræna excelsa*, Simarubeæ. Jamaica.

Preparations:

Extractum Quassiæ (U.S.P.).—*Dose:* 0.03 to 0.2 Gm. (½ to 3 grains).

Extractum Quassiæ Fluidum (U.S.P.).—*Dose:* 1.0 to 4.0 c.c. (¼ to 1 drachm).

Tinctura Quassiæ (U.S.P., B.P.).—10%. *Dose:* 2.0 to 8.0 c.c. (½ to 2 drachms).

Infusum Quassiæ (B.P.).—1% in *cold* water. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Liquor Quassiæ Concentratus (B.P.).—10%. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Chirata (U.S.P., B.P.).—The entire plant of *Swertia Chirata*, Gentianeæ. Northern India.

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[1] Gentian contains a small amount of Tannin; not enough to make it astringent, but sufficient to cause a decoloration with iron.

The most important preparations are marked ⁂.

Preparations:

Extractum Chiratæ Fluidum (U.S.P.).—*Dose:* 2.0 to 4.0 c.c. (½ to 1 drachm).

Tinctura Chiratæ (U.S.P., B.P.).—10%. *Dose:* 2.0 to 8.0 c.c. (½ to 2 drachms).

Liquor Chiratæ Concentratus (B.P.).—50%. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Infusum Chiratæ (B.P.).—5%. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Taraxacum (U.S.P., B.P.).—*Dandelion.*—The root of *Taraxacum officinale*, Compositæ. Temperate zone.

Preparations:

Extractum Taraxaci (U.S.P., B.P.).—As pill excipient.

Extractum Taraxaci Fluidum (U.S.P., B.P.).—*Dose:* 4.0 to 15.0 c.c. (1 to 4 drachms).

⁂ *Elixir Taraxaci Compositum* (N.F.).—With aromatics. As flavor.

Succus Taraxaci (B.P.).—*Dose:* 4 to 8 c.c. (1 to 2 drachms).

Nux Vomica.—See page 175.

II. Astringent Bitters.

With these, tannin is a prominent ingredient, whilst volatile oils are present only in small quantity, if at all. The preparations can be mixed with water.

Cascarilla (U.S.P., B.P.).—The bark of *Croton Eluteria*, Euphorbiaceæ. Bahama. *Dose:* 0.6 to 2.0 Gm. (10 to 30 grains).

Infusum Cascarillæ (B.P.).—5%. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Tinctura Cascarillæ (B.P.).—20%. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Cinchona.—See page 350.

* **Condurango.**—The bark of *Marsdenia Condurango*, Asclepiadeæ. Ecuador. Said to have a specific effect in carcinoma and ulcer of the stomach.

Preparations:

* *Extractum Condurango Fluidum.*—*Dose:* 1.0 to 1.5 c.c. (15 to 25 minims).

⁂ *Vinum Condurango.*—1 : 10. *Dose:* 4 c.c. (1 drachm).

Serpentaria (U.S.P., B.P.).—*Virginia Snakeroot.*—The rhizome and roots of *Aristolochia Serpentaria* and of *A. reticulata*, Aristolochiaceæ. United States.

Preparations:

Extractum Serpentariæ Fluidum (U.S.P.).—*Dose:* 0.6 to 2 c.c. (10 to 30 minims).

Tinctura Serpentariæ (U.S.P., 10%) [B.P., 20%].—*Dose:* 2.0 to 8.0 c.c. (½ to 2 drachms).

Liquor Serpentariæ Concentratus (B.P.).—50%. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Cimicifuga (U.S.P., B.P.).—*Black Snakeroot, Black Cohosh.*—The rhizome and roots of *Cimicifuga racemosa*, Ranunculaceæ. North America.

Preparations (made with strong alcohol and not miscible with water):

Extractum Cimicifugæ (U.S.P.).—*Dose:* 0.06 to 0.3 Gm. (1 to 5 grains).

Extractum Cimicifugæ Fluidum (U.S.P., B.P.).—*Dose:* 2.0 to 4.0 c.c. (½ to 1 drachm).

Tinctura Cimicifugæ (U.S.P., 20%) [B.P., 10%]—*Dose:* 2.0 to 8.0 c.c. (½ to 2 drachms).

Cuspariæ Cortex (B.P.).—*Angostura Bark, Cusparia.*—The bark of *Cusparia febrifuga*, Rutaceæ. Tropical South America. *Dose:* 0.6 to 2.5 Gm. (10 to 40 grains).

* Not official.

The most important preparations are marked ⁂.

III. Aromatic Bitters.

These contain both aromatic oils and bitter principles, but no tannin. Their alcoholic preparations cannot be mixed with water without turbidity (or filtering).

Calamus (U.S.P.).—*Sweet Flag.*—The rhizome of *Acorus Calamus*, Aroideæ. Europe and North America.

Preparations:

Extractum Calami Fluidum (U.S.P.).—*Dose:* 1.0 to 4.0 c.c. (¼ to 1 drachm).

Aurantii Amari Cortex (U.S.P.) [*Aurantii Cortex Siccatus* and *Recens*, B.P.].—The rind of the fruit of *Citrus vulgaris* (*Citrus Aurantium*, var. Bigaradia, B.P.), Rutaceæ. Cultivated in subtropical countries.

Preparations:

Extractum Aurantii Amari Fluidum (U.S.P.).—*Dose:* 2.0 to 4.0 c.c. (½ to 1 drachm).

⁂ *Tinctura Aurantii Amari* (U.S.P., B.P.).—20%. *Dose:* 4.0 to 8.0 c.c. (1 to 2 drachms).

Infusum Aurantii (B.P.).—5%. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Infusum Aurantii Compositum (B.P.) contains other aromatics. *Dose* as the infusion; also enters into Syrupus Aromaticus, Syr. Aurantii, and Vin. Aurantii (B.P.).

Absinthium (U.S.P.)—*Wormwood.*—The leaves and tops of *Artemisia Absinthium*, Compositæ. Europe.

Preparations:

* *Oleum Absinthii.*—Prep. by distillation. *Dose:* 0.05 to 0.1 c.c. (1 to 2 drops).

* *Infusum Absinthii.*—1 : 16. *Dose:* 30 to 60 c.c. (℥j to ij).

* *Absinthe.*—A liqueur consisting essentially of a solution of the oil in alcohol, of a strength of about 50%, with the addition of aromatics and coloring-matter. Ordinary amounts have effects analogous to those of alcohol, but if taken in excessive quantities, it induces mania and epileptiform conditions.

* **Achillea.**—*Yarrow.*—The herb of *Achillea millefolium*, Compositæ. Northern temperate zone. *Dose:* 2 to 4 Gm.

Humulus.—Also acts as bitter. For Materia Medica see page 227.

* **Panax.**—*Ginseng.*—The root of *Panax quinquefolium*, Araliaceæ, very highly valued by the Chinese, belongs to this series. So do *other species* of Panax and Aralia.

IV. Other "Bitters" Used in Domestic Medicine

are the following: Cnicus Arvensis, Æsculus glabra, Agrimonia Eupatoria, Plantago major, Scrophularia nodosa, Lappa officinalis, Adiantum pedatum, Coptis trifolia, Eupatorium purpureum, Fraxinus, Viburnum prunifolium, Sarracenia purpurea, Saxifraga Pennsylvanica, Pentstemon pubescens, Cynoglossum officinale, Asimina triloba, Menispermum Canadense, Gratiola virginica, Dipsacus sylvestris, Cephalanthus occidentalis, Ambrosia bidentata, Geum rivale, Lycopus Virginicus, Menyanthes trifolia, Polyporus officinalis, Prinos verticillata, Sabbatia campestris, Scutellaria latifolia, Simaruba officinalis, Marrubium vulgare, Berberis vulgaris, Boldoa fragrans, Chondrodendron tomentosum, Frasera Carolinensis.

These possess no advantage over the official Bitters.

V. Compound Bitters.

The taste and effect of bitters may be greatly enhanced by a proper blending. Indeed, these compound preparations almost always deserve the preference. The official mixtures have already been mentioned, viz.:

Tinctura Gentiana Composita (U.S.P., B.P.).—See page 712.

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* Not official.

The most important preparations are marked ⁂.

Elixir Aromaticum (U.S.P.).—See page 124.
Also the National Formulary:
Elixir Gentianæ (*Detannata*).—See page 712.
Elixir Taraxacum Compositum.—See page 713.
To these may be added:
* *Tinctura Amara* (N.F.).—*Dose:* 4 to 8 c.c. (1 to 2 drachms).
* *Vinum Aurantii Compositum* (N.F.).—*Dose:* 5 to 15 c.c. (2 to 4 drachms).

VI. Aromatics, Carminatives, and Condiments.

Here belong in the first place the oils distilled from the Aromatic Bitters. Many of the members of this group have already been mentioned under Flavors (see p. 122). The preparations of the Aromatics are of course immiscible with water. In addition to the Aromatics enumerated in the subjoined table (pp. 716 and 717), the following drugs of other groups act also as carminatives:

Myrrha. See page 689.
Asafetida. See page 685.
Valeriana. See page 685.
Camphora. See page 468.
Capsicum. See page 696.

The following mixtures may be taken as types:
⁂ *Mistura Magnesiæ et Asafœtidæ* (N.F.).—Magnesium Carbonate 5%, Tinct. Asafetida 7.5%, Tinct. Opium 1%. *Dose:* 2 to 8 c.c. (½ to 2 drachms).
⁂ *Tinctura Capsici et Myrrhæ* (N.F.).—Capsicum 3%, Myrrh 12.5%. *Dose:* 0.6 to 2 c.c. (10 to 30 minims).

(C) VEGETABLE CATHARTICS.

I. MANNER OF ACTION.

All vegetable irritants increase peristalsis when taken by mouth. However, those which have been classed as cutaneous irritants produce, when taken internally, a more marked effect upon the stomach, leading to vomiting; others act more specifically as carminatives; while still others tend to produce nephritis. These cannot be used in practice to affect peristalsis. The term "vegetable cathartic" is therefore restricted to those which irritate the intestine in a somewhat specific manner, with a much lesser action, if any, on skin, stomach, or kidneys.

The *reason for this peculiar limitation* of their irritant action to the intestinal canal depends upon their solubility or on certain phenomena of decomposition, both brought about by the alkaline reaction of the intestine.

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* Not official.
The most important preparations are marked ⁂.

TABLE OF AROMATICS, CARMINATIVES, AND CONDIMENTS.

NAME.	DERIVATION.	FAMILY.	HABITAT.	DOSE:		PREPARATIONS.[1]		DOSE:	
				Metric (Gm.).	Apoth.	Name.	Preparation.	Metric (Gm.).	Apoth.
Sassafras . . .	Root-bark of Sassafras variifolium.	Laurineæ.	North America.	1 to 4	¼ to 1 dr.	Oleum Sassafras.		0.06 to 0.3	1 to 5 min.
Caryophyllus (Cloves) . .	Unexpanded flower of Eugenia aromatica.	Myrtaceæ.	Tropics.	0.3 to 1.5	5 to 25 gr.	*Oleum Caryophylli*		0.06 to 0.3	1 to 5 min.
Pimenta (Allspice)	Nearly ripe fruit of Pimenta officinalis.	Myrtaceæ.	Tropical America.	0.3 to 1.5	5 to 25 gr.	Oleum Pimentæ.		0.06 to 0.3	1 to 5 min.
Piper (Black Pepper) . . .	Unripe fruit of Piper nigrum.	Piperaceæ.	Tropics.	0.3 to 1.5	5 to 25 gr.	Oleoresina Piperis.	Extraction with Ether and evaporation.	0.015 to 0.06	¼ to 1 gr.
						Piperinum.		0.06 to 0.6	1 to 10 gr.
Myristica (Nutmeg)	Seed of Myristica fragrans.	Myristicaceæ.	Tropics.	0.3 to 1.5	5 to 25 gr.	Oleum Myristicæ.	5% of the oil.	0.06 to 0.2	1 to 3 min.
						Spiritus Myristicæ.		2 to 4	½ to 1 dr.
Macis (Mace)	The covering (arillode) of the above.			0.3 to 1.5	5 to 25 gr.				
Cinnamomum	Bark of Cinnamomum Saigonicum, C. Zeylanicum, and C. Cassia.	Laurineæ.	Tropics.	0.3 to 1.5	5 to 25 gr.	Pulvis Aromaticus.		0.6 to 2.0	10 to 30 gr.
						Tinctura Cinnamomi.	10%.	4 to 8	1 to 2 dr.
						Extractum Aromat. Fluid.	From aromatic powder.	0.6 to 2	10 to 30 min.
						Oleum Cinnamomi.		0.06 to 0.3	1 to 5 min.
						Spiritus Cinnamomi.	10% of the oil.	0.6 to 2	10 to 30 min.
						Aqua Cinnamomi.	Saturated.	Flavor.	
Zingiber (Ginger)	Rhizome of Zingiber officinale.	Scitamineæ.	India.	0.3 to 1.5	5 to 25 gr.	*Tinctura Zingiberis.*	20%.	1 to 4	¼ to 1 dr.
						Syrupus Zingiberis.	3%.	2 to 8	½ to 2 dr.
						Extr. Zing. Fluid.	Alcohol.	0.3 to 1	5 to 15 min.
						Oleoresina Zing.	Extraction with Ether and evaporation.	0.03 to 0.12	½ to 2 gr.
						Trochisci Zing.	Each = 0.2 Gm.	Ad libitum.	

Cardamomum	Fruit of Elettaria repens.	Scitamineæ.	India.	0.3 to 1.5	5 to 25 gr.	Tinctura Cardamomi.		4 to 8	1 to 2 dr.
						Tinctura Cardamomi Comp.		8 to 15	2 to 4 dr.
Mentha Piperita and Viridis, see p. 122.									
Anisum (Anise)	Fruit of Pimpinella Anisum.	Umbelliferæ.	Southern Europe, Egypt, and Western Asia.	0.6 to 2.0	10 to 30 gr	Oleum Anisi. *Spiritus Anisi.*	10% of the oil.	0.06 to 0.3 4 to 8	1 to 5 min. 1 to 2 dr.
Illicium (Star Anise) . . .	Fruit of Illicium verum.	Magnoliaceæ.	Northern Anam.	0.6 to 2.0	10 to 30 gr				
Coriandrum (Coriander) .	Fruit of Coriandrum sativum.	Umbelliferæ.	Central Asia and Southern Europe.	0.6 to 2.0	10 to 30 gr	Oleum Coriandri.		0.06 to 0.3	1 to 5 min.
Fœniculum (Fennel) . .	Fruit of Fœniculum capillaceum.	Umbelliferæ.	Central Asia and Southern Europe.	0.6 to 2.0	10 to 30 gr	Oleum Fœniculi. Aqua Fœniculi.		0.06 to 0.3 Ad libitum.	1 to 5 min.
Carum (Caraway)	Fruit of Carum Carvi.	Umbelliferæ.	Central and Western Asia.	0.6 to 2.0	10 to 30 gr	Oleum Cari.		0.06 to 0.3	1 to 5 min.
Anethum (Dill)	Fruit of Peucedanum graveolens.	Umbelliferæ.	Middle and Southern Europe.	0.6 to 2.0	10 to 30 gr	*Oleum Anethi.		0.06 to 0.3	1 to 5 min.
		Many other plants of the order Umbelliferæ contain similar carminative oils.							
*Zedoaria . .	Tuber of Curcuma Zedoaria.	Scitamineæ.	India.	Like Ginger.					
*Galanga . . .	Rhizome of Alpinia officinarum.	Scitamineæ.	China.						

The *dose* of the aromatic drugs in powder (or infusion) is 0.3 to 1.5 Gm. (5 to 25 grains); of the oils, 0.06 to 0.3 c.c. (1 to 5 minims); of the spirits, 2 to 4 c.c. (30 to 60 minims).

[1] The more important are in italics.

* Not official.

Thus, castor oil and croton oil become active only when their fatty acids are liberated; croton oil contains some free acid and is therefore pustulant also on the skin. The group of "resins" are insoluble in water, but are also decomposed by alkalies, and become soluble at this time.

The reason why they do not cause nephritis is to be sought in the fact that the decomposition products become again inactive in the circulation. These drugs are *never corrosive*. The greater number are not even toxic to cells. When necrotic changes are found, these are the result of the violent inflammation (just as in the case of colchicin or of arsenic).

The *inflammatory action* usually affects only the sensory endings which have to do with the setting-up of peristaltic impulses; but the action may extend deeper, and involve the muscles, etc. The result of the irritation is an *increased peristalsis*, with consequent hyperemia. If the irritation is violent, it also produces pain (colic or "griping").

The quickened peristalsis will cause expulsion of the intestinal contents before there is time for the absorption of liquid which normally occurs (especially from the large intestine). The stools are consequently soft to semifluid or liquid, according to the violence of the peristalsis.

It follows from this, that with moderate doses the fluid of the stools is not derived from the tissues; none the less, these become drier, since they are prevented from replacing the water lost by urine and respiration. Doses which produce inflammation may, however, cause an inflammatory exudate to be thrown into the intestine.

If the vegetable cathartics are injected into the blood instead of being taken by the mouth, some of them produce increased peristalsis, others do not. The effect, when it exists, is probably due to their being excreted into the intestine. They are therefore never used by *hypodermic application* in practice. Such injections would also be very painful, and may lead to abscess-formation. It is characteristic of these vegetable cathartics that, when they are administered by the mouth, they produce a more certain and more extensive action if given in the form of preparations of the crude drugs, than is produced by the isolated active principles.

This is due to the fact that the latter are to a large extent soluble and absorbable. They therefore irritate the stomach and often do not reach the intestinal canal. In the crude drugs they are protected by the presence of various colloid substances which prevent their irritant action and solution. For this reason, they reach the intestine without very much change, and since they remain here for a longer time, may develop their full action.

II. CLASSIFICATION.

The vegetable cathartics may be divided into three pharmacologic groups:

(*A*) *The Neutral Oils:*
These include *Croton Oil* and *Castor Oil.*
(*B*) *The Anthracene Derivatives.*—Cathartin, chrysarobin, and their acids. These are the active principles of *Senna, Rhubarb, Rhamnus, Cascara Sagrada, Aloes.*
(*C*) *The Resinous Anhydrids:*
Jalapin, Scammonin, Elaterin, Podophyllin, Colocynthin, Gamboge, Euonymin.

(A) The Neutral Oils.—Croton Oil.—The active irritant principle of this is a fatty acid—*crotonolic acid.* In the oil this exists mainly in the form of a glycerid, which is entirely inactive. Some, however, is free, so that the oil acts as a very strong irritant in any situation. On the skin it produces pustulation. In the intestine, the glycerid is split like any other fat, and the liberated acid may develop its action to the fullest degree, and is a most violent "drastic" purgative.

Oleum Tiglii (U.S.P.) [**Ol. Crotonis**, B.P.].—*Croton Oil.*—A fixed oil expressed from the seeds of *Croton tiglium*, Euphorbiaceæ. India and Philippines. Soluble in 60% alcohol. Should be at least two years old. *Dose:* 0.015 to 0.12 c.c. (¼ to 2 drops), on a lump of sugar, slice of bread or of lemon.

Linimentum Crotonis, B.P. (see p. 708).

Castor Oil contains the glycerid of an analogous acid—*ricinoleic acid;* the action of this is similar to that of crotonolic acid, but very much less violent. Since it does not exist at all in free form in the oil, this is perfectly bland and non-irritant to the skin or stomach.

In China it is used as an article of diet. The properties of Castor Oil were known to Herodotus; but Croton Seeds were first described in the middle of the sixteenth century.

⁂ **Oleum Ricini** (U.S.P., B.P.).—*Castor Oil.*—A fixed oil expressed from the seeds of *Ricinus communis*, Euphorbiaceæ. Cultivated. *Soluble* in an equal volume of alcohol. *Dose:* 8.0 to 60.0 c.c. (¼ to 2 oz.).

The taste of castor oil is very nauseant to many persons. It is then best administered in the form of capsules.

Mistura Olei Ricini (B.P.).—A 40% emulsion flavored with Orange Flower and Cinnamon. *Dose:* 30 to 60 c.c. (1 to 2 oz.).

(B) Anthracene Derivatives:

A number of derivatives of anthracene, $C_{14}H_{10}$, possess an irritant action, and form the active principles of this class of drugs. The best studied of the isolated products are *chrysarobin* and *chrysophanic acid.* In the pure form there

The most important preparations are marked ⁂.

are entirely too irritant to be useful as cathartics; their use is restricted to the skin (see p. 698). They are, however, contained in rhubarb, together with emodin, cathartin, cathartic acid, and others, which are also anthracene derivatives. The active principles of senna, of cascara, etc., are all similar, but not identical. Little is known about their exact composition. They have probably never been isolated in pure form, since they are very subject to decomposition. The active principle of aloes—aloin—also belongs to this series. It also is not identical in the different varieties of aloes.

The cathartic action of these principles is materially regulated by the colloid substances of the crude drugs. Their action is so mild that they never produce inflammation. This makes them especially valuable when the use of a purgative is to be continued.

A number of these anthracene derivatives color the urine.

It may be well to advise the patient of this fact. *Coloration of the urine* may also be important to the physician in showing whether his medicine is being taken, or what the patient is using in addition. The following are the most important:

The substances of this group, especially rhubarb and senna, produce a yellow-brown color in acid, purplish-red in alkaline, urine. *Logwood* (Hematoxylon) does not color acid urine, but produces a reddish or violet color in alkaline urine. Santonin gives a yellow color to acid urine, with a yellow foam; if the urine is made alkaline it gives a very pronounced pink. Picric acid gives yellow color in both acid and alkaline urine. The various coal-tar products give a brownish-black color.

⁂ **Senna** (U.S.P.).—The leaflets of *Cassia acutifolia* [**Senna Alexandrina**, B.P.] (Alexandria Senna) or *Cassia angustifolia* [**Senna Indica**, B.P.] (India or Tinnevelly Senna), Leguminosæ. Eastern and Central Africa and India; cultivated. *Dose:* 5 to 15 Gm. (1 to 4 drachms).

Senna produces considerable griping. This may be almost abolished, without greatly reducing the strength of its action, by first exhausting it with strong alcohol.

The ⁂ *Extractum Sennæ Fluidum Deodoratum* (N.F.) is made in this manner.

The stools occur about five to twelve hours after its administration.

The best preparation is an extemporaneous infusion. This must not be boiled very long, else the activity suffers.

The following are *official:*

Extractum Sennæ Compositum (U.S.P.).—Contains Aromatics. One-half alcohol. *Dose:* 4 to 10 c.c. (1 to 2½ drachms).

⁂ *Infusum* [*Mistura*, B.P.] *Sennæ Compositum* (U.S.P., B.P.).—(*Black Draught.*) *Dose:* 30 to 60 c.c. (1 to 2 ozs.). An excellent preparation.

Contains per cent.: Senna 6, Manna 12, Magnes. Sulph. 12, Fennel 2.

⁂ *Pulvis Glycyrrhizæ Compositus* (U.S.P., B.P.).—*Compound Licorice Powder. Dose:* 2 to 8 Gm. (½ to 2 drachms) stirred in water.

Contains per cent.: Senna 18, Sulphur 8, and Glycyrrhiza, Fennel, and Sugar.

Confectio Sennæ (U.S.P., B.P.).—Contains per cent.: Senna 10, Cassia Fistula 16, Tamarind, Prune, and Coriander. *Dose:* 4 to 8 Gm. (1 to 2 drachms).

⁂ *Syrupus Sennæ* (U.S.P., B.P.).—Contains 15%. *Dose:* 8 to 30 c.c. (¼ to 1 oz.).

The most important preparations are marked ⁂.

Infusum Sennæ (B.P.).—10% ; flavored with Ginger. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Liquor Sennæ Concentratus (B.P.).—50% ; contains Ginger. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Tinctura Sennæ Composita (B.P.).—20% ; with Aromatics. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

* *Species Laxantes* (N. F.) (*St. Germain Tea*).—Per cent.: 40 Senna, 10 Cream of Tartar; Elder flowers, Fennel, and Anise. *Dose:* 4 to 15 Gm. (1 to 4 drachms), as infusion.

Cassia Fistula (U.S.P.) [**Cassiæ Pulpa**, B.P.].—The fruit of *Cassia Fistula*, Leguminosæ. East India. *Dose:* 4 to 30 Gm. (1 to 3 drachms).

Rheum (U.S.P.) [**Rhei Radix**, B.P.].—The root of *Rheum officinale* and other undetermined species. Polyganaceæ. China; cultivated. (The species of Rhubarb cultivated in this country (*Rheum palmatum*) are devoid of cathartic properties.)

The Russian Rhubarb is that exported *via* Russia, whilst the so-called Chinese or East India Rhubarb comes by water.

Records of the use of rhubarb in China date back to 2700 B. C.

The *principal constituents* are the cathartic principles: *Chrysophanic Acid*, $C_{15}H_{10}O_4$ (arises from chrysophan, $C_{27}H_{30}O_{14}$, when the root is boiled); *Emodin*, $C_{15}H_{10}O_5$; *Rhein*, $C_{15}H_{10}O_6$. (Note the close relations in the composition of these principles.) *Bitter Resins:* Erythroretin, Phæoretin, and Aporetin; *Rheotannic Acid; Rheumic Acid;* Lime Oxalate, Starch, Sugar, Pectin, etc.

Whilst the active principles show a general similarity with those of senna, certain of its constituents modify its action. The rheotannic acid tends to produce a secondary constipation. The bitter resins give it a stomachic action. On this account, and also because its taste is less disagreeable, it is preferred to senna for convalescents. It also produces less colic, and is generally milder. It acts in eight to ten hours.

Preparations:

Pilulæ Rhei (U.S.P.).—Each contains 0.2 Gm. (3 grains) of powdered Rhubarb. *Dose:* as stomachic, 1; as purgative, 3 to 5.

⁂ *Pulvis Rhei Compositus* (U.S.P., B.P.).—(*Gregory's Powder.*) Rhubarb, 25; Magnesia, 65; Ginger, 10. *Dose:* 2 to 4 Gm. (½ to 1 drachm).

⁂ *Pilulæ Rhei Compositæ* (U.S.P.).—Each contains: Rhubarb, 0.13 Gm. (2 grains); Aloes, 0.1 Gm.; Myrrh, 0.06 Gm.; and Oil of Peppermint. *Dose:* as stomachic, 1; as purgative, 2 to 4.

⁂ *Pil. Rhei Composita* (B.P.) contains the same ingredients. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Extractum Rhei (U.S.P., B.P.).—By extraction with four-fifths alcohol and evaporation. *Dose:* 0.2 to 1 Gm. (3 to 15 grains).

Infusum Rhei (B.P.).—5%. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Extractum Rhei Fluidum (U.S.P.).—Four-fifths alcohol. *Dose:* 1 to 4 c.c. (¼ to 1 drachm).

Liquor Rhei Concentratus (B.P.).—50%. *Dose:* 1 to 4 c.c. (¼ to 1 drachm).

Tinctura Rhei (U.S.P.).—10%. Cardamom, 2%. Glycerin and two-thirds alcohol. *Dose:* 2 to 15 c.c. (½ to 4 drachms).

⁂ *Tinctura Rhei Aromatica* (U.S P., 20%) [B.P., 10%].—Aromatics; one-half alcohol. *Dose:* 4 to 12 c.c. (1 to 3 drachms).

⁂ *Syrupus Rhei Aromaticus* (U.S.P.).—Aromatic Tincture, 1; Syrup, 5½. *Dose:* 15 to 30 c.c. (½ to 1 ounce).

Tinctura Rhei Dulcis (U.S.P.).—10%. Glycyrrhiza and Aromatics; one-half alcohol. *Dose:* 15 to 30 c.c. (½ to 1 ounce).

Mistura Rhei et Sodæ (U.S.P.).—Sod. bicarb., 3.5% ; Fl. Ext. Rhubarb,

* Not official.

The most important preparations are marked ⁂.

1.5%; Fl. Ext. Ipecac, 0.3%; Sp. Peppermint, Glycerin, and Water. *Dose:* 8 to 60 c.c. (¼ to 2 ounces).

Syrupus Rhei (U.S.P.).—Fl. Ext. Rhubarb, 10%; Pot. Carb., 1%; Cinnamon, Glycerin, and Syrup. [B.P., 5%; with coriander.] *Dose:* 2 to 8 c.c. (½ to 2 drachms).

Rhamnus Purshiana (U.S.P.) [**Cascara Sagrada**, B.P.].—*Cascara Sagrada.*—The bark of *Rhamnus Purshiana*, Rhamneæ. Pacific Coast of North America.

When the bark is first collected it is emetic. After two years' keeping this action is lost, and the cathartic quality is acquired. The active principles are: *Cascarin*, which is a cathartin or emodin principle; bitter resins, etc.

The above also applies to:

Frangula (U.S.P.).—*Buckthorn.* The bark of *Rhamnus Frangula.* Europe and Northern Asia.

Preparations:

Extractum Frangulæ Fluidum (U.S.P.).—*Dose:* 2 to 8 c.c. (½ to 2 drachms).

Extractum Rhamni Purshianæ Fluidum (U.S.P.).—One-half alcohol. *Dose:* 1 to 4 c.c. (¼ to 1 drachm).

⁂ *Elixir Rhamni Purshianæ* (N.F.).—1 : 4. *Dose:* 4 to 15 c.c. (1 to 4 drachms).

Aloe.—The inspissated juice of the leaves of

Aloe Barbadensis (U.S.P., B.P.).—*Barbadoes* or *Curaçoa Aloes.*—*Aloe vera*, Liliaceæ. Island of Barbadoes.

Aloe Socotrina (U.S.P., B.P.).—*Aloe Perryi.* Eastern Africa.

Many other varieties are on the market, but are of less value. Aloes was known to the Greeks.

The active principles are the Aloins. These are different for each variety, but are all anthracene derivatives.

⁂ *Aloinum* (U.S.P., B.P.) *Aloin*, is usually Barbaloin, but sometimes Socaloin. It is soluble in 60 parts of water or 30 parts of alcohol. *Dose:* 0.03 to 0.12 Gm. (½ to 2 grains).

The action of aloes and aloin shows several peculiarities. In small doses they act as stomachics. Their cathartic action is greatly aided by bile, so that they may have very little effect in obstructive icterus. They occasion but little colic. On account of the intensely bitter taste, they are best given in the form of pills. They produce a comparatively strong congestion of the pelvic organs, and are therefore emmenagogue. This action forms a contraindication to their use in pregnancy, or when there are hemorrhoids. They are most useful in chronic constipation in middle life.

The *dose* of Aloes is 0.3 to 0.6 Gm. (½ to 10 grains).

Preparations:

Aloe purificata.—Aloes softened by heating and addition of alcohol, strained and dried. This is the form which enters into most of the pills. *Dose* as for Aloes.

Extractum Aloes (U.S.P.) [——— *Barbadensis*, B.P.].—A dried watery extract. *Dose:* 0.03 to 0.2 Gm. (½ to 3 grains).

Tinctura Aloes (U.S.P., 10%) [B.P., 2.5%].—Licorice; ½ alcohol. *Dose:* 1 to 4 c.c. (¼ to 1 drachm).

Tinctura Aloes et Myrrhæ (U.S.P.).—10% each, licorice, three-fourths alcohol. *Dose:* 4 to 10 c.c. (1 to 2 drachms).

Decoctum Aloes Compositum (B.P.).—½% of Extract of Aloes, with Myrrh, Pot. Carbonate, and Aromatics. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Aloes enters into a large number of pills, usually in combination with some carminative. Besides those enumerated here, into Pil. Cathart. Co., Rhei Co., etc. It is also the chief ingredient of very many proprietary pills.

The most important preparations are marked ⁂.

In the following *U. S. Pills*, only the content of Aloes will be given; the *dose* is one to four:

⁂ *Pilulæ Aloes:* 0.13 Gm. (2 grains).
Pilulæ Aloes et Asafœtidæ: 0.09 Gm. (1⅓ grains).
⁂ *Pilulæ Aloes et Ferri:* 0.07 (1 grain).
Pilulæ Aloes et Mastiche: 0.13 (2 grains).
⁂ *Pilulæ Aloes et Myrrhæ* 0.13 (2 grains).
⁂ *Pilulæ Aloini, Strychninæ et Belladonnæ*, N.F.—Each pill contains Aloin, 0.013 Gm. (⅕ grain); Strychnin, 0.0005 Gm. ($\frac{1}{100}$ grain); Ext. Belladonna, 0.008 Gm. (⅛ grain).

The following *B. P. Pills* are official (the *Dose* is 0.25 to 0.5 Gm.—4 to 8 grains):

⁂ *Pilula Aloes Barbadensis:* 50%.
⁂ *Pilula Aloes et Ferri:* 20% Aloes, 10% Iron Sulphate.
Pilula Aloes Socotrinæ: 50%.
Pil. Aloes et Asafœtidæ: 25% each.
⁂ *Pil. Aloes et Myrrhæ:* 45% Aloes, 25% Myrrh.

(C) Group of Anhydrids.—Although the constitution of these principles is not at all understood, their chemic reactions, as well as their physiologic effects, show so many points of similarity as to cause them to be placed in one group.

The active principles are for the most part resinous (*i. e.*, soluble in alcohol, but slightly soluble in water), often glucosids, and on chemic manipulation (probably hydration) they yield acids. The latter are much less active.

It is characteristic of these principles that they are *not as effective when given pure* as when they are mixed with some extractive, as in the "resins" (alcoholic extracts precipitated by water), or as preparations of the crude drug. This is due, in some cases, to their being somewhat soluble, and therefore absorbed in the stomach.

The drugs of this series are generally *much more irritant* than the anthracene derivatives. They belong to the *drastic or hydragogue cathartics.* It is difficult to limit their action sufficiently to make them useful as aperients, and they are only employed when very active catharsis is essential. They should be avoided with children. The principal ones are the following:

Jalapa (U.S.P., B.P.).—*Jalap.*—The tuberous root of *Ipomœa Jalapa*, Convolvulaceæ. Eastern Mexico. *Active principles:* Convolvulin and Jalapin. *Dose:* 0.3 to 1 Gm. (5 to 15 grains).

Jalap acts in about three hours. It is often given with calomel.

Preparations:

Extractum Jalapæ (U.S.P., B.P.).—The dried alcoholic extract. *Dose:* 0.12 to 0.5 Gm. (2 to 8 grains).

Resina Jalapæ (U.S.P., B.P.).—Extraction with alcohol and precipitation of the resin with water. *Dose:* 0.06 to 0.3 Gm. (1 to 5 grains).

The most important preparations are marked ⁂.

⁂ *Pulvis Jalapæ Compositus* (U.S.P., B.P.).—Jalap 1, Pot. Bitartrate 3. *Dose:* 1 to 4 Gm. (¼ to 1 drachm).

Tinctura Jalapæ (B.P.).—20%. Three-fourths alcohol. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Scammonium (U.S.P., B P.).—*Scammony.*—A resinous exudation from the living root of *Convolvulus Scammonia*, Convolvulaceæ. Western Asia. *Active principle:* Jalapin. *Dose:* 0.3 to 1 Gm. (5 to 15 grains).
Preparations:

⁂ *Resina Scammonii* (U.S.P., B.P.).—Extraction with alcohol and precipitation of the resin with water. *Dose:* 0.06 to 0.3 Gm. (1 to 5 grains).

Pilula Scammonii Composita (B.P.).—Contains Ginger. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Pulvis Scammonii Compositus (B.P.).—Contains Ginger. *Dose:* 0.6 to 1.3 Gm. (10 to 20 grains).

Podophyllum (U.S.P., B.P.).—*May Apple, Mandrake.*—The rhizome and roots of *Podophyllum peltatum*, Berberideæ. North America. *Active principles:* Podophyllotoxin and Picropodophyllin. *Dose:* 0.3 to 1.2 Gm. (5 to 20 grains).
Preparations:

Extractum Podophylli (U.S.P.).—Made with four-fifths alcohol. *Dose:* 0.12 to 0.6 Gm. (2 to 10 grains).

Extractum Podophylli Fluidum (U.S.P.).—Made with four-fifths alcohol. *Dose:* 0.3 to 1.2 c.c. (5 to 20 minims).

⁂ *Resina Podophylli* (U.S.P., B.P.).—(*Podophyllin.*) By extraction with alcohol and precipitation of the resin by water. *Dose:* 0.008 to 0.03 Gm. (⅛ to ½ grain).

Colocynthis (U.S.P.) [**Colocynthidis Pulpa**, B.P.].—*Bitter Apple.*—The fruit of *Citrullus Colocynthis*, Cucurbitaceæ. Asia, Africa, Greece, and Spain. *Active principle:* Colocynthin. The decomposition product of this glucosid—colocynthein—is also active. *Dose:* 0.1 to 0.5 Gm. (2 to 8 grains).
Preparations:

Extractum Colocynthidis (U.S.P.).—Made with one-half alcohol. *Dose:* 0.03 to 0.1 Gm. (½ to 2 grains).

⁂ *Extractum Colocynthidis Compositum* (U.S.P., B.P.).—Contains Colocynth, Aloes, Scammony, Cardamom, and Soap. *Dose:* 0.3 to 1.0 Gm. (5 to 15 grains).

Pil. Colocynthidis Composita (B.P.).—Contains the same active ingredients as the Pulvis. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

⁂ *Pilulæ Catharticæ Compositæ* (U.S.P.).—Each pill contains:

	GRAMS.	GRAINS.
Compound Extr. Colocynth	0.08	1¼
Calomel	0.06	1
Extract Jalap	0.03	½
Gamboge	0.015	¼

Dose: One to four.

⁂ *Pilulæ Catharticæ Vegetabiles* (U.S.P.).—Each pill contains:

	GRAMS.	GRAINS.
Compound Extract Colocynth	0.06	1
Extract of Hyoscyamus	0.03	½
Extract of Jalap	0.03	½
Extract of Leptandra	0.015	¼
Extract of Podophyllum	0.015	¼
Oil of Peppermint	0.008	⅛

Dose: One to four.

Elaterinum (U.S.P., B.P.).—A neutral principle obtained from *Elaterium*

The most important preparations are marked ⁂.

(B.P.), a substance deposited by the juice of the fruit of *Ecballium Elaterium* (Squirting Cucumber), Cucurbitaceæ. Western Asia, Northern Africa, and Southern Europe; cultivated. *Dose:* 0.003 to 0.005 Gm. ($\frac{1}{20}$ to $\frac{1}{12}$ grain).

Preparations:

Trituratio Elaterini (U.S.P.).—1 : 10. *Dose:* 0.03 to 0.06 Gm. (½ to 1 grain).

Pulvis Elaterini Compositus (B.P.).—1 : 40 in Sugar of Milk. *Dose:* 0.06 to 0.25 Gm. (1 to 4 grains).

Bryonia (U.S.P.).—The root of *Bryonia alba* and of *B. dioica*, Cucurbitaceæ. Central and Southern Europe. *Active principles:* The glucosids Bryonin and Bryonidin. *Dose:* 0.6 to 4.0 Gm. (10 to 60 grains).

Preparation:

Tinctura Bryoniæ (U.S.P.).—10% alcohol. *Dose:* 8 to 15 c.c. (2 to 4 drachms).

Cambogia (U.S.P., B.P.).—*Gamboge.*—A gum resin obtained from *Garcinia Hanburii*, Guttiferæ. Anam, Camboja, and Siam. *Active principle:* Gambogic Acid. Since this is fairly soluble, even the gum-resin is irritant to the stomach, so that it should always be given in pill form. *Dose:* 0.06 to 0.3 Gm. (1 to 5 grains).

Pilula Gambogiæ Composita (B.P.).—Contains Aloes. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Leptandra (U.S.P.).—*Culver's Root.*—The rhizome and roots of *Veronica Virginica*, Scrophularineæ. United States. *Active principle:* The glucosid Leptandrin.

Preparations:

Extractum Leptandræ (U.S.P.).—Made with three-fourths alcohol. *Dose:* 0.06 to 0.2 Gm. (1 to 3 grains).

Extractum Leptandræ Fluidum (U.S.P.).—Made with three-fourths alcohol. *Dose:* 1 to 4 c.c. (¼ to 1 drachm).

Iris (U.S.P.).—*Blue Flag.*—The rhizome and roots of *Iris versicolor*, Irideæ. North America. *Active principle* not well known.

Preparations:

Extractum Iridis (U.S.P.).—Made with alcohol. *Dose:* 0.06 to 0.2 Gm. (1 to 3 grains).

Extractum Iridis Fluidum (U.S.P.).—Alcohol. *Dose:* 0.6 to 2 c.c. (10 to 30 minims).

(D) SUMMARY OF CATHARTICS.

Cathartics or *Evacuants* are drugs which cause an increase in peristalsis.

I. MANNER OF ACTION.

For innervation of the intestine, etc., see pages 205 to 207.

The intestines are to some extent under the control of the central nervous system; *e. g.*, a sudden fright may cause evacuation of the bowels; melancholia is frequently the cause of constipation. However, this central influence is quite exceptional, and cannot be utilized therapeutically, except in so far as regulation of the bowels by habit is concerned. All the remedial measures depend upon local actions.

Pharmacologically, these may be divided into: (*a*) Measures which produce peristalsis by *directly* stimulating the efferent nerve-muscle chain; (*b*) measures which produce peristalsis *reflexly* in virtue of an irritation, or by swelling the volume of the intestinal contents.

The former (*a*) comprise the alkaloids physostigmin, pilocarpin, etc. They are not useful in practice.

II. CLASSIFICATION.

Before taking up the practically used cathartics in detail, it may be well to classify them according to their clinical characters; *i. e.*, mainly by the strength of their action.

Such a classification is by no means sharp, for the same drug may belong to different groups, according to the amount used, and according to other conditions. The classification is rendered still more complicated by the fact that different authors do not use the same nomenclature, but often apply the same term to very different actions.

The following table gives what is probably the most useful clinical classification:

1. **Laxatives or Aperients:** Those which increase peristalsis only moderately, producing somewhat more frequent stools, of almost normal consistency, and this without causing notable irritation. They are active in *doses* of 10 Gm. or over:

Fruits, Manna, Honey, etc.; mechanical means (massage, charcoal, electricity, etc.); Sulphur, Magnesia, Carminatives, Bland Oils (Olive, Cotton-seed, Linseed, etc.).

(Small doses of Cascara, Senna, Castor Oil, Rhubarb, and Ipecac are also laxative.)

2. **Purgatives:** Those which increase peristalsis actively, causing frequent semi-fluid stools.

(A) **Simple Purgatives:** Active in *doses* of 0.2 to 1 Gm. These cause considerable colic and irritation:

Aloes, Rhubarb, Senna, Cascara, Castor Oil, Bile, Calomel, small doses of drastics.

(B) **Saline Purgatives:** Active in doses of about 10 Gm. Rather profuse, watery stools, with practically no irritation or griping:

Sulphate of Sodium or Magnesium, Sodium Phosphate, Magnesium Citrate, Potassium Bitartrate, Rochelle Salt, etc.

3. **Drastics:** Produce watery stools, with much inflammation. Large doses are apt to set up an enteritis. Active in *doses* of less than 0.1 Gm.:

Elaterium, Colocynth, Jalap, Scammony, Gamboge, Podophyllin, Croton Oil, the stronger Mercurials, and Antimony Sulphid.

The drastics and salines are called *hydragogues*, since they remove much fluid.

Those which quicken peristalsis particularly in the duodenum remove bile from the intestine by lessening its reabsorption, and constitute the clinical class of **cholagogues** (see p. 731). This comprises Aloes, Rhubarb, Mercurials, Podophyllin, Euonymin, Sod. Salicylate or Phosphate, Acid. Nitrohydrochlor. Dilut., Bile.

III. LAXATIVE MEASURES.

This division includes those measures which increase the bulk of the intestinal contents; those which act as mechanical irritants; physical measures; enemata; sulphur and magnesia.

(A) Substances Used to Increase the Bulk of the Intestinal Contents:

Liquid: Water (direct or indirect).
Oils.
Solids: Indigestible food or insoluble medicines.

Large quantities of pure **water** may be given for this purpose, but this will be more effective in the shape of *carbonated drinks*—soda-water, etc. *Lemonade* acts partly by its acid. These liquids are more effectual if taken *cold*, since cold in itself stimulates peristalsis. (Water should not be taken in the form of liquids containing tannin—such as tea or red wines.) Water may also be introduced in the form of *succulent vegetables* and fruits,—apples, tomatoes, melons, etc.,—which, however, act in part like other fruits, by their pectin, acid, etc.

The liquid in the intestines may be increased *indirectly* by preventing its absorption through the use of *salts*.

The bland, fatty **oils**, in quantities larger than can be digested, form very efficient laxatives. They can, however, only be taken by patients with good digestion.

The same holds of **indigestible food.**

Constipation is very often caused by deficiency in the indigestible portion of the diet. It is a mistake to suppose that a diet which is entirely digested and absorbed is the best. Animals, for example, are entirely unable to subsist on such food, and in feeding-experiments it is frequently necessary to add cellulose in the form of filter-paper to maintain them in good condition. The functionation of the intestine is necessary to the organism; perhaps in effecting the removal of bile and other toxic products formed in the body, as well as of the toxins generated in the intestine by bacteria.

Cases of constipation arising from this cause may, of course, be at once benefited by a change of the diet to one containing more indigestible material, such as many vegetables rich in cellulose. The desirable limit may, however, be exceeded.

Of medicinal agents which act in this way, *Manna* may be mentioned.

Manna (U.S.P.).—A concrete saccharine exudation from *Fraxinus Ornus*, Oleaceæ. Mediterranean coast. The chief constituents are Mannit (90%), Glucose, Fraxin, Mucilage, Resin. *Dose:* 15 to 60 Gm. (½ to 2 ozs.) as infusion.

(**B**) This class borders closely on the **mechanical irritants,** since the distention of the bowels constitutes in itself a source of mechanical irritation. However, the irritation is increased when the indigestible particles are sharp or gritty, as the seeds of fruit (strawberries, figs, etc.) or as the husks of grain (oatmeal).

Fruits, fresh or stewed, are generally laxative. They act in part by the water which they contain; partly by the non-absorbable pectin substances which swell the bulk of the feces; partly by acid salts which exert a chemic irritation; partly by their sugar, which acts, by osmosis, like a saline cathartic.

Charcoal acts purely mechanically.

Carbo Ligni (U.S.P., B.P.).—*Wood Charcoal.*—Made by heating wood without access of air. *Dose:* 1 to 4 Gm. (15 to 60 grains).

Carbo Animalis (U.S.P.), *Animal Charcoal* (Bone-black), is used for decolorizing.

Carbo Animalis Purificatus (U.S.P.) has been exhausted with HCl, and may be used in acid liquids for the same purpose.

(**C**) Of **physical measures** which have a laxative effect may be mentioned *massage*, *moderate exercise*, all kinds of *cold baths*, or *electricity*.

The latter may be applied by laying a large electrode on the abdomen and connecting another to the rectal tube, through which salt solution is flowing into the intestine. In this way the stimulation covers the greatest area.

(**D**) **Enemata** (*clysters*) are injections into the rectum. Any distention of the rectum will set up *peristaltic contraction* in this organ, and stimulate reflexly even the higher portions of the intestine. Pure water will suffice for this, but the effect will, of course, be greater if some irritant be added.

To secure the maximum motor effect, the injection must be used cold, and in fairly large quantity: Adults a pint, quart, or more; children according to age (at a year, an ounce, and about ½ ounce more for each year). Water and bland oils are also often used by high injection.

The *irritants* which are most commonly used in clysters are: Soap, castor oil, or molasses,. 1 : 8; salt, 1 : 16; turpentine, 1 : 20 (emulsified with one egg-yolk).

Glycerin is sometimes given pure in doses of ʒj to iv, as also in the form of suppositories.

⁂ *Suppositoria Glycerini:* **Each contains 6 Gm.; made with sodium stearate.**

Enemata have an *advantage* over cathartics taken by mouth, in that they may be made absolutely non-irritant, and may therefore be used in conditions in which the other cathartics are positively contraindicated. On the other hand, they soon lose their efficiency.

If the purpose of the enema be merely to *soften hardened scybala*, they would be used warm, in copious quantities, preferably with soap; or as decoctions of mucilaginous substances.

Enemata also have other uses: For *local effects* on the rectal mucous membrane (astringents, etc.); for the *removal of parasites* (see p. 739); and as a method of *introducing medicine and nourishment* (see p. 757).

The dose of medicines per rectum is about twice as much as by mouth.

For local effects, the astringents are used in the same strength as on other mucous membranes (see p. 682). When the injection is to be retained, it must be small in amount, warm, and non-irritant. (The irritation may be diminished by the addition of boiled starch.)

IV. IRRITANT CATHARTICS.

Whilst the number of substances which may irritate the intestine is very great, those which can be employed in practice as cathartics are rather limited, for various reasons.

An ideal cathartic should produce profuse and soft, but not too numerous evacuations, without pain, tenesmus, or nausea, and without leaving any tendency to constipation.

Irritants which cause a marked *irritation of the stomach* are excluded altogether. This is one reason why the pure principles are not employed. As has been said, these are usually protected by colloids in the preparations made from crude drugs. The cathartics in ordinary use are so chosen that they cause little or no gastric disturbance in individuals with healthy digestion. However, when this is impaired, it may be necessary to administer them in "intestinal capsules" (see p. 80).

All those which have a fairly strong action cause considerable *colic* or *tenesmus*. This is the necessary accompaniment of a violent peristalsis, and if the latter is desired, the former must be taken into the bargain. All that the physician can do is to inform the patient that it is a sign that the medicine is doing its work.

The tendency to *congestion of the pelvic organs* is also a necessary consequence of intestinal irritation. Where this is strongly contraindicated, the non-irritant salines, or enemata, must be used.

All irritant cathartics leave a *tendency to constipation*, which may become very annoying, especially when they are used habitually. This is seen especially with rhubarb, less with senna or cascara. It is not often serious, and rarely necessitates an increase in the dose.

The mercurial purgatives produce a tendency to *nephritis*, which contraindicates their continued use.

The intestinal irritants may be divided into mechanical, vegetable, and mineral. The first have already been summarized on page 727.

Mineral Irritants:

Acids.—It will be remembered that free acids cannot be employed for this purpose, since they do not reach the intestine. Practically the only form is as Cream of Tartar, which acts largely as a saline.

Salines—see page 726.

Sulphur acts only in the measure in which it is converted into soluble sulphid by the carbonates of the intestine. Since the latter are limited in amount, the strength of action is within large limits independent of the dose. Sulphur merely softens the stools, and is therefore particularly useful in piles.

Of metals, *mercury* is the only one which is useful. It is best given as calomel, together with a vegetable irritant, to insure its prompt expulsion.

The special uses of the various *vegetable cathartics* have already been partly discussed in the preceding sections, and will receive further mention in the following.

Several **alkaloids,** whilst not themselves cathartic, are often useful in this connection.

Belladonna and *Morphin*, especially the former, relieve spasm from overstimulation of the intestine, and are therefore useful in constipation as the result of intestinal spasm (lead colic). Belladonna also serves to regulate the irritant action of the vegetable cathartics, and in this way lessens griping (Aloin, Belladonna, and Strychnin (see p. 723) is quite a favorite preparation; the rôle of the *Strychnin* is not understood.)

V. ACTION OF DRUGS ON THE BILE.

The influence of bile on peristalsis is considerable. Its presence in the intestine is quite irritating; its absence will favor constipation. A class of preparations acting upon the flow of bile would therefore be very desirable. Starting from the observation that the stools after certain cathartics have a darker or greenish color, the older therapeutists referred this to an increased secretion of bile, and distinguished these substances as *cholagogues*—remedies which increase the flow of bile. When these were subjected to physiologic experimentation on animals with biliary fistulæ, the results were at first contradictory, owing to the fact that the flow of bile shows considerable variations naturally, and these observations did not extend over a sufficient time to eliminate this factor. Recent unobjectionable experiments have finally settled this question. According to these, the only true cholagogues, increasing both the volume of bile and the absolute quantity of bile-salts, are bile and salicylates, especially the former.

For this purpose, dried ox-bile may be given, two pills containing 0.25 Gm. each, three times a day, preferably coated with salol.

Bile salts have a typical digitalis action on the heart.

The action of salicylates is quite small, and they must be used in doses of 5 Gm. per day.

Fel Bovis (U.S.P.).—*Ox-gall.*—The fresh bile of the ox.
⁂ *Fel Bovis Purificatum* (U.S.P., B.P.).—Ox-gall evaporated after addition of alcohol. *Dose:* see above.

The other drugs formerly classed as "cholagogues"—mercury salts, the saline and drastic purges—are simply active cathartics or antiseptics. The dark color of the stools is due to their carrying the *normal* quantity of bile through the intestine without giving time for the normal change of the bile pigment to the lighter fecal pigment; or to diminution of the bacterial action which causes this change. The action of acids (especially nitromuriatic) and acid salts was not investigated in these researches. It is conceivable that they may cause, reflexly, an emptying of the gall-bladder.

(E) USE OF CATHARTICS.

Cathartics are perhaps the most ancient method of internal medication, and were for a long time practically the only method. Even the Greeks used the same word, *φαρμακειν*, both for internal medication in general and for the use of cathartics in particular. The present English word *physic* is similarly applied.

1. Cathartics are still used in many different conditions; most frequently, however, in constipation, particularly **habitual constipation.**

The *consequences* of habitual constipation need not be gone into in this place. They arise mainly from the absorption of toxic products, the result of bacterial putrefactive processes going on in the intestine. These substances are by no means uniform, and many have never been isolated. Some are toxins, others ptomains of the muscarin series; H_2S is also poisonous; so is indol, the appearance of which in the urine is usually taken as an index to this intestinal putrefaction. Since the greater number of these products tend to increase peristalsis, they are to some extent their own antidotes, and are perhaps even useful in normal individuals. They only become objectionable if their production exceeds the ordinary limits.

The first object in the treatment of habitual constipation is to *remove the cause*, if possible. This cause will very frequently be found in *faulty habits;* irregularity in going to stool, in time of eating or quality of food, insufficient exercise, etc. These must be corrected if they exist, and this will often contribute more to a cure than any drugs.

Another cause of constipation is *atony* of the intestinal or abdominal muscles, either congenital or acquired. In these cases resort should first be had to mechanical means—massage and electricity. If these mechanical means are not sufficient, or for any reason cannot be applied, the pharmacologic remedies are indicated. The latter are also to be used when the cause of the constipation lies in the *pain* from hemorrhoids, or the *pressure* from tumors, or pregnancy.

In *using cathartics* the rule should always be to *employ the mildest remedy* which will accomplish the result. One reason for this is that soft, not liquid, stools are desired; but, further, a "habit" is quite readily acquired, so that the intestines will require stronger and stronger stimuli, and the usual cathartics gradually lose their efficiency. If the treatment has been begun with mild measures, stronger ones are left for later use if necessary. The habitual use of very irritant cathartics is also quite apt to engender a chronic enteritis. This mistake of taking strong purgatives continually is one made only too frequently.

Perhaps the best cathartics in habitual constipation are those of the cathartin group—senna, cascara, rhubarb, or aloes. There is really no objection to the prolonged use of these mild cathartics.

Occasionally one encounters patients with just sufficient knowledge to lead them to think that the taking of purgatives is against nature, and therefore necessarily detrimental; and who will object very seriously to using them. While this reasoning is very good when the intestines are normal, it cannot stand when anything is abnormal, as in the case of atony. An atonic condition of the intestine requires the habitual use of cathartics, just as an atonic condition of the ciliary muscle requires the use of glasses. Both are harmful in health, both are indicated in disease.

The *time of day* in which cathartics are to be given is determined by the length of time which they require to produce their action.

The vegetable cathartics or calomel require, with moderate doses, ten to twelve hours; larger doses, five hours; and the drastics may even act in three hours. The cathartic salts act more promptly—*i. e.*, in one to three hours.

It is therefore customary to give the vegetable cathartics, as also calomel, in the evening before going to bed, so that they will act in the morning. However, if the constipation is the cause of insomnia, as sometimes happens, it is better to give them in the morning. The cathartic salts are usually given in the morning.

2. Purgatives frequently lead to the arrest of **diarrheas.**

This might at first view appear paradoxical. But one need only remember that diarrhea is a conservative process intended to remove the irritant agent, and it will be plain that, unless excessive, the employment of a cathartic is simply a support of nature. One must also remember that peristaltic impulses always travel in a downward direction. The irritation caused by a mass of putrefying material may set up quite a violent peristalsis below this point, while the mass itself may be but little affected. A cathartic, on the other hand, starting peristalsis high in the intestine, will sweep out the mass and remove the materies morbi.

3. Cathartics are indicated in those infectious diseases in which the seat of the **infection** is **in the intestinal canal.** If the bacteria have not yet penetrated into the

tissues, their expulsion may abort the infective process, or will in all cases diminish it. Cathartics are in this way "intestinal antiseptics."

4. Cathartics are useful **to remove poisons**—bacterial or chemic—both from the intestinal canal itself and from the body. They will be useful in preventing the further absorption of a toxic agent, as well as the reabsorption of such poisons as are excreted into the intestine.

5. A further indication for the use of cathartics is **to soften the stools.** This is required in diseases of the rectum, especially hemorrhoids; also to prevent any tendency to straining during stool (in aneurysm, or hernia, or tendency to apoplexy).

6. Another use is in **dropsical conditions** of all kinds, to remove water from the body. This also affords relief to the kidneys, so that cathartics may be useful in *nephritis*.

7. Irritant cathartics are of value in **congestions,** especially of the brain, through changing the distribution of the blood. Since they draw more blood to the abdomen, they lower the general blood pressure.

8. Cathartics are also used **to lower temperature** in fever. This action is not sufficiently explained. They do not affect the normal temperature.

Contraindications.—There are several contraindications to the use of cathartics, especially to the stronger kinds. All inflammatory conditions of the abdominal organs (peritonitis, gastro-enteritis, etc.) preclude the administration of intestinal irritants. Pregnancy and menstruation are contraindications to the use of the stronger cathartics, since the hyperemia may lead to abortion or excessive menstrual flow. General debility or tendency to collapse, as also threatened intestinal hemorrhage, are further contraindications, as also toxic spasm of the intestine.

Experience has established which of the cathartics best meet the *special indications.* In *habitual constipation*, where the object is to produce the least irritation possible, rhubarb, senna, and cascara sagrada or aloes are the best. In *diarrhea*, those which produce large and watery stools with the minimum of irritation are preferred; *i. e.*, the saline cathartics or castor oil. *To soften the feces*, sulphur and enemata deserve preference. For the *removal of liquid* from the body, the best would be the saline cathartics with the addition of either senna or rhubarb. For the *removal of* *poisons* or of other toxic products from the alimentary canal, one would use the most active—the drastic purgatives.

(F) ANTHELMINTICS:

i. e., Remedies against Intestinal Parasites.

I. GENERAL CONSIDERATIONS.

An active peristalsis will tend to remove intestinal parasites, as well as the other intestinal contents. Active cathartics are therefore necessarily *Vermifuges*—*i. e.*, drugs which expel parasites. But these parasites, when in good condition, are endowed with remarkable faculties of maintaining their position in the intestines—by traveling in the direction opposite to peristalsis, or by fixing themselves to the intestinal wall by means of suckers or hooks, or by their serrated margins, etc. It therefore becomes necessary to lower their vitality. This may be done to some extent by appropriate diet. But this is rarely sufficient, and it is generally necessary to employ drugs which will paralyze them—*Vermicides.* Since the latter necessarily present some danger to the host as well, it is desirable that they should be used in the smallest doses. For this reason it is well to give them their maximum efficiency by preceding them with a course of diet which lowers the resistance of the parasite without affecting the host. The vermicides but rarely kill the parasites; these usually recover if they remain in the intestine. It is therefore very necessary to follow the vermicide by an active cathartic, usually a drop of croton oil.

II. PRELIMINARY DIETARY MEASURES.

A limitation of the proteids of the diet is generally regarded as injurious to the parasite, but care must be taken not to carry this so far as to weaken the resistance of the patient. Carbohydrates may be allowed in any amount. Mechanical irritants—vegetables rich in fiber; the seeds of strawberries, blackberries, or figs; the husks of grain, etc. —are very useful. So are "sharp" articles of diet—condiments, especially those of the mustard group, strongly salted meat, etc. At the time when the vermicide is taken, the intestinal canal should be fairly empty, so that the parasite will not be protected by the contents. The remedies are therefore usually given before breakfast, and no food is taken for several hours after. This unfortunately increases the tendency to the absorption of the poison, and to the local irritation. Vomiting may occur and render a repetition of the whole cure necessary. It has been attempted to circumvent this difficulty by combining the principles with tannin, but this lessens their action. The best that can be done is to inclose them in gelatin capsules.

III. VERMICIDES.

The substances which are toxic to intestinal parasites are in general toxic to all forms of protoplasm. The class of intestinal antiseptics are all to some extent vermicidal, but can scarcely be introduced in sufficient amount to kill the parasites without injuring the host. Special qualities are necessary for this end: The remedy must be absorbed to the smallest possible extent, since its absorption would not only render it deleterious to the patient, but would also prevent its reaching the lower portions of the intestine and acting on the parasites found there. On the other hand, it must be capable of penetrating the resistant, often chitinous, covering of these worms. This combination can only be secured with *volatile* poisons, whose vapors permeate the intestinal canal and penetrate into the parasites before there is time for an extensive absorption. The latter is also retarded by the presence of fixed oils; and, accordingly, it will be found that the majority of vermicides are solutions in a fixed oil, of some volatile poison, essential oils, or volatile alkaloids, etc. From this volatility of the active principles, it follows necessarily that these drugs are *not very stable;* the more so since these principles also undergo chemic changes very readily. This uncertain activity has thrown mistrust on the whole class of anthelmintics. The pharmaceutic extracts or isolated principles share this instability, although to a less degree.

Finally, it is more than probable that these parasites, as most other forms of life, show *peculiar susceptibility* to certain poisons. There is some hope that further research will bring forth specific vermicides. At present, the following data have been gathered from empirical observations:

The most efficient for *Tapeworms* are Male Fern (especially for Bothriocephalus); Pelletierin (especially for Tænia);

and Kosotoxin; for *Round Worms*, Santonin and Spigelia. *Thread Worms* are treated most efficiently from the rectum by enemata.

It may be well to mention that the vermicides are *under no circumstances absolutely safe.* They should never be given unless the parasites or their eggs are actually demonstrated in the feces. This is also the time when treatment offers the greatest chance of success.

(A) Vermicides for Tapeworm.

1. **Turpentine** (see p. 688) is used in domestic medicine in tablespoon doses. It is uncertain, and produces such violent irritation of the alimentary canal and kidneys that it is not to be advised. The same holds true of **Chloroform.** *Thymol, Salol, Naphtol,* etc., have not been subjected to sufficient trial to permit an estimate of their value.

2. **Pumpkin** or *Melon Seed,* fresh or at least not over a year old, is eaten in half-ounce or ounce doses, on the day preceding the regular treatment. They are not sufficiently active themselves, but serve to support other measures. It is not known in what their action resides, but they contain a large amount of fat, with traces of volatile oil and resins. The fresh "milk" of the cocoanut is also said to be anthelmintic.

⁂ *Pepo* (U.S.P.).—*Pumpkin Seed.* The seed of *Cucurbita Pepo,* Cucurbitaceæ; cultivated.

3. **Aspidium** (U.S.P.) [*Filix Mas,* B.P.].—*Male Fern.*—The rhizome of *Dryopteris* (Aspidium) *Filix mas* and *D. marginalis,* Filices. North America, Northern Asia, and Europe. *Dose:* 2.0 to 6.0 Gm. (30 to 90 grains).

The active ingredients are Filicic Acid, a volatile oil, and a fixed oil. All seem to be necessary, but the filicic acid is the most active. On keeping the drug, this passes readily into its anhydrid, Filicin, which is absolutely inactive. The official

⁂ *Oleoresina Aspidii* [*Extractum Filicis Liquidum,* B.P.], made by extraction with ether and evaporation, seems the only rational preparation. *Dose:* 1.0 to 4.0 c.c. (¼ to 1 drachm), preferably in capsules.

Overdoses cause especially nervous phenomena: General depression, coma, and convulsions, collapse, and sometimes death; there is also usually a gastroenteritis. Disturbances of vision are not uncommon. The nerve-fibers are degenerated. The chance of absorption is stated to be increased by the presence of an excess of fixed oil in the intestines, so that it is *contraindicated* to use castor oil as cathartic.

4. **Granatum** (U.S.P., B.P.).—*Pomegranate.*—The bark of the stem and root of *Punica Granatum,* Lythrarieæ. Cultivated in subtropical countries. *Dose:* 2.0 to 6.0 Gm. (½ to 1½ drachms), usually given as infusion.

The *active constituents* are two volatile alkaloids—Pelletierin (= Punicin) and Isopelletierin (= Granatonin). There are, further, two less active alkaloids—Methylpelletierin and Pseudopelletierin. The drug also contains a large proportion (20%) of a peculiar tannin—Punicotannic Acid.

Decoctum Granati Corticis (B.P.).—20%. *Dose:* 15 to 60 c.c. (½ to 2 ozs.). The large amount of tannin in this preparation is very irritant to the stomach, and frequently circumvents the purpose of the drug by causing vomiting. To avoid this, and also to give greater uniformity, the

⁂ *Pelletierinum tannicum* has been introduced. It is an insoluble powder, and is given in the *dose* of 0.5 to 1.0 Gm.

The most important preparations are marked ⁂.

Overdoses produce results similar to those of Filix mas, but less violent. Applied to the eye, it produces miosis, as does also arecolin.

5. **Cusso** (U.S.P., B.P.).—*Kousso, Brayera.*—The female inflorescence of *Hagenia Abyssinica*, Rosaceæ. Abyssinia. *Dose:* 10.0 to 20.0 Gm. (2½ to 5 drachms). (The male flowers are powerfully emetic, and therefore useless as vermicides.)

The *active principle* is given as Kosotoxin, a non-nitrogenous neutral principle; also resins (Coussin and Cosin) and volatile oils, which probably aid. *Preparation:*

Extractum Cusso Fluidum (U.S.P.).—Made with alcohol. *Dose:* 4 to 15 c.c. (1 to 4 drachms).

Kamala (U.S.P.).—*Rottlera.*—The glands and hairs from the fruit capsules of *Mallotus Philippinensis*, Euphorbiaceæ. India, China, and Philippines. *Dose:* 10 Gm. (2½ drachms). The active ingredient appears to be *Rottlerin.*

* **Areca.**—The fruit of *Areca Catechu*, Palmæ. Southern Asia. Contains vermicidal volatile alkaloid (Arecolin). Areca is only used in veterinary medicine.

(B) Vermicides for Round Worms (Ascaris lumbricoides).

All the remedies for Tape-worm are to some extent effective; and the same dietetic measures, as well as subsequent purge, are necessary.

Santonica (U.S.P.).—*Levant Wormseed.*—The unexpanded flowerheads of *Artemisia pauciflora*, Compositæ. Turkestan. *Dose:* to 4 Gm. (60 grs.). Now obsolete, since it has no advantage over its chief constituent:

⁂ **Santoninum** (U.S.P., B.P.).—*Santonin.*—$C_{15}H_{18}O_3$. A neutral principle, occurring as colorless crystals. Nearly insoluble in water, soluble in 40 parts of alcohol. Best given in the form of

⁂ *Trochisci Santonini* (U.S.P.).—Each contains 0.03 Gm. (½ grain). [B.P. = 1 grain]. *Dose:* for children, 1 to 4; for adults, 10; U.S.P. [5, B.P.]; given in the evening.

The *action* of santonin is not well understood, but there is no doubt that it drives the ascarides into the lower intestine, from which they can be dislodged by cathartics, especially calomel.

The santonin itself is practically insoluble, but in the intestine it is converted into the soluble and absorbable santonin-sodium. This is excreted in the urine as santogenin, giving the liquid a lemon-yellow color when acid, carmine-red when alkaline. This absorption determines various systemic phenomena.

Doses as small as 0.1 Gm. cause "yellow vision"—*i. e.*, white light has at first a violet, then a yellowish-green hue, and these colors tint the entire field of vision. (Exactly the same phenomenon is sometimes seen with amyl nitrite.) The power of seeing in dim light is also lessened. It has been demonstrated that these effects are peripheral, and the theory is advanced, based on some experimental data, that santonin impairs the reproduction of the visual purple and violet, which are at first used very rapidly. There is no truth in the statement that it discolors the media of the eye.

Still larger doses have often led to *toxic symptoms.* These comprise headache, vertigo, weakness, somnolence, *convulsions*, fall of temperature, delirium, vomiting, and diarrhea.

The treatment would be symptomatic. Santonin has also been tried against *epilepsy*, with very little success.

The following are used only in domestic medicine:

Spigelia (U.S.P.).—*Pinkroot.*—The rhizome and roots of *Spigelia Mari-*

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* Not official.

The most important preparations are marked ⁂.

landica, Loganiaceæ. Southern United States. Said to contain a volatile oil, volatile alkaloid, and a bitter principle and resin.

Extractum Spigeliæ Fluidum (U.S.P.).—One-half alcohol. *Dose:* 2 to 8 c.c. (½ to 2 drachms).

Chenopodium (U.S.P.).—*American Wormseed.*—The fruit of *Chenopodium ambrosioides* (variety anthelminticum), Chenopodiaceæ. Naturalized in United States. *Dose:* 1.0 to 2.0 Gm. (15 to 30 grs.). The active principle is probably a volatile oil—

Oleum Chenopodii (U.S.P.).—*Dose:* 0.1 to 0.6 c.c. (2 to 10 minims).

Tanacetum (see p. 692).

(C) Vermicides for Thread Worms (Oxyuris).

These are usually treated most efficiently by the rectal injection of various irritants. The rectum is first treated with injections of iron, tannin, or bitters, to limit the secretion of mucus, and is then irrigated with solutions or emulsions of salt (℥ss to pt.), aloes (ʒj to pt.), or turpentine (ʒij to pt.), etc. Mercury salts are sometimes used as injection or suppository, but are dangerous.

CHAPTER XXXI.

EMOLLIENTS AND DEMULCENTS.

(A) SKIN DISEASES.

EMOLLIENTS and Demulcents are drugs which soften, "relax," protect, and "soothe" the parts to which they are applied; in other words, drugs which lessen irritation. The term *emollient* is restricted more to those used on the skin, *demulcent* to those applied to mucous membranes. No very sharp distinction can be drawn between these, and many belong to both classes; but, as a rule, the fats are used as emollients, the gums as demulcents.

These substances act by being chemically and physically indifferent. Their chemic affinities are very weak. Since they are either insoluble, as the fats, or possess very large molecules, as the colloids, they do not exert any salt action. They may therefore be left in intimate contact with cells and tissues without causing irritation. When applied to exposed surfaces, they serve to form a protective coating, and prevent the access of irritants—whether chemic, as by gases or solutions; mechanical, as by dust; or bacterial; or, finally, through the effects of drying. In this protection lies their main value.

The **oily emollients** are valuable, in addition, by penetrating into the squames of the stratum corneum, and rendering this more pliable. They reinforce in this way the natural fat of the skin, prevent roughness and "cracks" from wind, from cold weather, from skin diseases, etc.

A further use of emollients is for the *conveyance of medicines.* As has been pointed out on page 137, non-volatile substances are not absorbed by the skin from aqueous solutions, but from solutions in oil. The rapidity of this absorption can be greatly increased by rubbing the ointment *into* the skin. The fat can be made to penetrate quite deeply, and may be demonstrated microscopically in the lymph-channels.

The true fats are gradually oxidized and disappear. But the mineral oils —petroleum, etc.—are practically incapable of oxidation, remain in the subcutaneous tissue for a long time, and, acting as foreign bodies, may prove a source of irritation. The animal and vegetable fats, therefore, deserve the preference when penetration is to be secured.

Glycerin (see p. 743) resembles the ordinary fats very closely. Its hygroscopic nature prevents it from drying. However, if used in concentrated solution on mucous membranes or open wounds, it withdraws water from the tissues and acts as a mild irritant. It is useful in this way as a purgative, being administered either as enema (1 or 2 drachms, undiluted) or as suppository. It is also useful as a demulcent, but its action does not extend beyond the stomach, since it is absorbed. It is capable of oxidation, and may be a source of energy. Its sweet taste has caused it to be used as a substitute for sugar in diabetes, but the sweetness is of a kind rather disagreeable to many persons.

If emollients are applied to open wounds or denuded surfaces, they serve the function of an artificial epidermis, furnishing a protection against injurious agents. The same result can be secured by covering the surface with a thin pellicle of an impermeable substance, as by applying *collodion* or *resinous tinctures*, and allowing the solvent to evaporate; or by applying *plasters* or bandages. The latter cannot be discussed in this place. The plasters differ from other fats mainly in their firmer consistency. On this account they are much more slowly absorbed, and can be applied for a longer time. However, their action also differs from that of plain ointments in being more irritant. This is due partly to their preventing entirely all evaporation from the skin, partly also to small quantities of volatile oils contained in the resins from which they are prepared. They are frequently useful as mild counterirritants for the relief of pain, absorption of swellings, hastening of abscess formation, etc. They are also employed for the conveyance of drugs which are intended to act purely locally, and to be absorbed very slowly, such as Belladonna, Aconite, Capsicum, etc.

Adhesive plaster acts purely mechanically. Poultices are also largely emollient.

Another class of substances, exerting a similar action, but physically very different, are the *dusting-powders*. These could be arranged into several classes. The simple powders are very fine ("impalpable"), indifferent, insoluble, non-irritant powders, such as talcum, chalk, starch, lycopodium, etc. They form a covering, just as do the fats, and are also used to prevent friction. They absorb secretions by capillary action, and are therefore drying. The metallic oxids and carbonates are in addition somewhat astringent. The absorbability of toxic metals, even when in the form of insoluble salts, must not be lost sight of, and lead compounds should be avoided altogether. Bismuth salts, except perhaps the subgallate, are also dangerous if applied to open surfaces. The zinc oxid and carbonate are entirely unobjectionable.

Lycopodium.—The spores of *Lycopodium clavatum* and other species, Lycopodiaceæ. Northern Hemisphere. Used only as dusting-powder.

Demulcents.—If soothing substances are applied to the mucous membrane of the respiratory or alimentary tract, their action must be conceived as parallel to that on the skin. But it must be remembered that this action is exerted only by that portion of the substance which adheres to the walls—not by that contained in the lumen. The gums, possessing a greater degree of "stickiness," are therefore more effective in these situations than the oils, and are the most useful *demulcents*.

The quality of drying, which renders them inapplicable to the skin, does not, of course, come into play here; whilst there is no thick stratum corneum to be softened, as by oils.

One sees a beautiful illustration of these facts in the natural lubricants of body-coverings. Whilst the skin is normally covered with a thin layer of oil, the membranes of the interior of the body are moistened with mucus, which is a typical gummy demulcent.

The characteristic qualities of these colloids (*i. e.*, glue-like substances) are seen in their watery solutions.

"Solution" is perhaps a misnomer, for many do not exhibit the characters which are considered as distinctive of true solutions.

These "solutions," then, are more or less viscid, adhesive, non-irritant, comparatively impenetrable, and absorbed with difficulty, if at all. As has been said, mucus is a very typical demulcent, and the artificial demulcents are mainly useful when the natural mucus is deficient in quantity. Their ability to protect the membranes against irritants will be readily understood. In the alimentary canal they will be useful against all forms of *irritant poisons*, whether introduced from without or formed in the body, as in faulty digestion. Milk or eggs are effective in the former case. Colloids will also *delay the absorption* of other substances, and this determines their use in pills, capsules, etc., as well as the advantages of extracts over alkaloids, etc., in certain cases. On the other hand, this interference with absorption is objectionable when the drug is given hypodermically. The demulcents are also useful in disguising or moderating the taste of disagreeable substances.

A good instance of their action in lessening irritation is the addition of boiled starch to *enemata*, to secure their retention. In *inflammation of the respiratory passages*—bronchitis, laryngitis, and pharyngitis—such a protection of the inflamed mucous membrane against the irritation of bacteria, air, and drying, must be of the greatest importance. Theoretically one would be inclined to think that their action would be limited to the upper portions of the respiratory tract; but clinical experience has shown that this is by no means the case, and that their action extends to remote bronchi. It would seem very unlikely that they would be excreted here, as has been claimed. Their effect must be either reflex, or else they must reach these parts by gradually flowing to them.

MATERIA MEDICA.

I. Bland Fatty Oils.

These oils are liquid, insoluble in water or glycerin, very sparingly in alcohol, freely in chloroform, ether, volatile oils, or fats. The dose internally is from 1 to 8 ounces (30 to 250 c.c.).

*** *Oleum Olivæ* (U.S.P., B.P.).—*Olive Oil* (*Sweet Oil*).—The fixed oil expressed from the ripe fruit of *Olea Europæa*, Oleaceæ. Cultivated in warm climates. The best oil for internal use.

Oleum Amygdalæ Expressum (U.S.P., B.P.).—*Expressed Oil of Almond.* —A fixed oil expressed from Bitter or Sweet Almonds (see p. 745).

Oleum Lini (U.S.P., B.P.).—*Linseed* (*Flaxseed*) *Oil.*—Expressed from Linseed (see below).

*** *Oleum Gossypii Seminis* (U.S.P.).—*Cottonseed Oil.*—Expressed from the seeds of *Gossypium herbaceum* and other species, Malvaceæ. Cultivated. On account of its cheapness, it is especially adapted for external use.

Oleum Adipis (U.S.P.).—*Lard Oil.*—The liquid portion of lard.

Many other oils may also be used.

II. Other Liquid Emollients.

*** *Glycerinum* (U.S.P., B.P.).—*Glycerin.*—($C_3H_5(OH)_3$.)—A thick, colorless liquid, of a sweetish taste, obtained by the decomposition of fats or fatty oils (see p. 593). Specific gravity, 1.250. Soluble in water or alcohol. (An important use of glycerin is as a solvent—see p. 63).

Preparations: Glyceritum Amyli and Vitelli (see p. 744).
Suppositoria Glycerini (U.S.P., B.P.) (see p. 729).

Glycerin enters also into many other preparations as solvent.

*** *Acidum Oleicum* (U.S.P., B.P.).—*Oleic Acid.*—$H.C_{18}H_{33}O_2$ (see p. 587). A yellowish or brownish oily liquid, insoluble in water, soluble in alcohol. Usually quite impure, containing other fatty acids. Used principally as solvent for medicines intended to be absorbed from the skin.

*** *Petrolatum Liquidum* (U.S.P.) [*Paraffinum Liquidum*, B.P.].—A mixture of hydrocarbons, chiefly of the marsh-gas series, obtained from petroleum, and purified until it has the required color (Fuscum, Flavum, Album, Albissimum, etc.).

III. Semi-solid Fats.

These possess the character of the fatty oils, except that they are soft solids at ordinary temperature.

*** *Oleum Theobromatis* (U.S.P., B.P.).—*Cacao-butter.*—A *solid* fat expressed from the seed of *Theobroma cacao*, Sterculiaceæ. Central and South America. Used mainly for making suppositories.

Sevum.—*Suet* (U.S.P., B.P.).—*Mutton Suet.*—The internal fat of the abdomen of the Sheep (*Ovis aries*), purified by melting and straining.

Adeps (U.S.P., B.P.).—*Lard.*—The internal fat of the abdomen of the pig (*Sus scrofa*). Other animals also yield fats which are popularly supposed to have special advantages—dog fat, goose grease, etc. There appears to be no reason for preferring them to the more easily obtainable lard.

Animal fats become rancid quite rapidly. Hence all ointments are directed to be prepared from:

*** *Adeps Benzoinatus* (U.S.P., B.P.).—Made by digesting lard with gum benzoin. In this process it takes up a certain amount of the latter, and acquires the properties of balsams, besides increasing its own keeping qualities.

* *Butyrum*, *Butter*, is sometimes used as an ointment basis. Since it can not be salted for this purpose, it keeps very poorly.

*** *Adeps Lanæ Hydrosus* (U.S.P., B.P.).—The official substitute for *Lanolin*. The purified fat of sheep's wool, mixed with not more than 30% of water.

Adeps Lanæ (B.P.) is the same substance without water.

Wool-fat possesses a number of advantages as an ointment. It does not readily become rancid; it is absorbed with the greatest ease; and it is miscible with twice its weight of water. It consists mainly of cholesterins, together with some fatty acids.

IV. Soft Mineral Fats.

⁂ *Petrolatum Molle* (U.S.P.) [*Paraffinum Molle*, B.P.].—*Soft Petrolatum.*[1] A mixture of hydrocarbons obtained from petroleum, melting between 40° and 45° C.

**Petrolatum Album.*—The above, but bleached to a white color.

Petrolatum Spissum (U.S.P.).—*Hard Petrolatum.*—Melting between 45° and 51° C.

V. Substances of a Waxy Consistency.

These are used to increase the solidity of ointments (as in cerates).

Cetaceum (U.S.P., B.P.).—*Spermaceti.*—A solid fatty substance obtained from the sperm whale (Physeter macrocephalus). It consists mainly of a combination of Cetylic Alcohol with Palmitic Acid.

Acidum Stearicum (U.S.P.).—*Stearic Acid.*—$H.C_{18}H_{35}O_2$. Usually more or less impure; obtained by decomposing tallow. The commercial acid melts at 56° C.

Cera Flava (U.S.P., B.P.).—*Yellow Beeswax.*—Melts at 63° to 64° C.

⁂ *Cera Alba* (U.S.P., B.P.).—*Bleached Beeswax.* Melts at 65° C.

Paraffinum Durum (B.P.).—*Paraffin.*—A white waxy solid, a mixture of solid hydrocarbons obtained from Petroleum. The melting-point lies between 43° and 65° C.

VI. Resins.

These usually contain some essential oils, and therefore act as mild dermal irritants. They are used in cerates and plasters.

Resina (U.S.P., B.P.).—*Rosin, Colophony.*—The residue left after distilling the volatile oil from Turpentine.

Pix Burgundica (U.S.P., B.P.).—*Burgundy Pitch.*—The prepared black resinous exudation of *Abies excelsa*, Coniferæ. Europe.

Elastica (U.S.P.) [*Caoutchouc*, B.P.].—*India-rubber, Caoutchouc* (Para Rubber).—The prepared juice of various species of *Hevea*, Euphorbiaceæ. Tropical countries. Soluble in Chloroform, Carbon Disulphid, Turpentine, Petroleum Ether, and Benzol. Swells in ether without dissolving.

Combined with 10% of sulphur by heating, it gives *vulcanized rubber;* with 50%, ebonite.

* *Gutta-percha.*—The concrete juice of *Dichopsis gutta* and other trees of the same order, Sapotaceæ. South America. Properties are similar to those of Rubber.

VII. Compound Emollient Ointments and Ointment Bases.

Unguentum (U.S.P.).—Lard 80, Yellow Wax 20.

⁂ *Unguentum Aquæ Rosæ* (U.S.P., B.P.).—(Cold Cream.)—Spermaceti, White Wax, Expressed Oil of Almond, Rose Water, and Sodium Borate.

Ceratum (U.S.P.).—White Wax 30, Lard 70.

* *Resorbin.*—An emulsion of Almond Oil, said to be very readily absorbed.

⁂ *Glyceritum Amyli* (U.S.P., B.P.).—Starch 10, Water 10, Glycerin 80.

Glyceritum Vitelli (U.S.P.).—Yolk of egg 45, Glycerin 55.

Ceratum Cetacei (U.S.P.) [*Unguentum Cetacei*, B.P.].

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[1] This is identical with the commercial product known as "Vaselin."

* Not official.

The most important preparations are marked ⁂.

VIII. Official Plasters.

(The composition is that of the U.S.P. preparations.)

Emplastrum:	Base:	Medical Ingredient.
Ammoniaci cum Hydrargyro (U.S.P., B.P.)	Ammoniac, Lead Plaster.	Mercury, 20%.
Arnicæ (U.S.P.)	Resin Plaster.	Extr. Arnica Root, 33%.
⁂ *Belladonnæ* (U.S.P., B.P.)	Resin and Soap Plaster.	Alc. Extr. Bellad. Leaves, 20%
⁂ *Capsici* (U.S.P.)	Resin Plaster.	Oleoresin Capsicum.
Ferri (U.S.P.)	Olive Oil, Burgundy Pitch, and Lead Plaster.	Ferric Hydrate, 9%.
Hydrargyri (U.S.P., B.P.)	Lead Plaster.	Mercury, 33%.
⁂ *Cantharidis* (B.P.)	Yellow Wax, Lard, and Resin.	Cantharides, 35%.
⁂ *Ichthyocollæ* (Court Plaster)	Isinglass, etc., spread on taffeta (used as adhesive).	
Opii (U.S.P., B.P.)	Burgundy Pitch and Lead Plaster.	Extr. Opii, 6%.
⁂ *Picis Burgundicæ* (U.S.P., B.P.)	Burgundy Pitch, Olive Oil, and Yellow Wax.	
⁂ *Picis Cantharidatum* (U.S.P.) *Calefaciens* (B.P.)	Burgundy Pitch.	Cantharides, 8%.
⁂ *Plumbi* (U.S.P., B.P.) (Diachylon Plaster)	A soap of Lead and Olive Oil, made by boiling the latter with Lead Oxid.	
Plumbi Iodidi (B.P.)	Lead Plaster.	Lead Iodid, 10%.
⁂ *Resinæ* (U.S.P., B.P.) (Adhesive Plaster)	Resin, Lead Plaster, and Yellow Wax.	
Saponis (U.S.P., B.P.)	Soap and Lead Plaster.	
Menthol (B.P.)	Yellow Wax and Resin.	Menthol, 15%.

Liquor Sodii Silicatis (Water-glass), *Calcii Sulphas* (Plaster-of-Paris), and *Collodion* (see p. 69) can only be mentioned in this place as mechanical supports in bandaging.

IX. Demulcents: Oily Seeds.

These contain gum, oil, and starch. When rubbed with water, they form natural emulsions, which serve especially as emollients. For internal use they are taken as decoctions; *dose* ad libitum.

Amygdala Dulcis (U.S.P., B.P.).—*Sweet Almond.*—The seed of *Prunus Amygdalus* var. *dulcis*, Rosaceæ. Cultivated.

Emulsum Amygdalæ (U.S.P., 6 : 100) [B.P., 12 : 100].

Pulvis Amygd. Compositus (B.P.) contains Acacia and Sugar.

* *Cydonium.*—*Quince Seed.*—The seed of *Cydonia Vulgaris*, Rosaceæ. Cultivated.

⁂ **Linum** (U.S.P., B.P.).—*Linseed*, *Flaxseed*, and *Linum Contusum*

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* Not official.

The most important preparations are marked ⁂.

(B.P.), Crushed Linseed.—The seed of *Linum usitatissimum*, Lineæ. Cultivated. The use as poultice is mentioned on page 701.

Hemp seed and rape seed are similarly demulcent.

Seeds and tubers rich in starch may be used as demulcents in the form of decoction. They are enumerated under nutrients.

X. Gums.

(Gums are insoluble in alcohol!)

⁂ *Acacia* (U.S.P.) [*Acaciæ Gummi*, B.P.].—*Gum-Arabic*. A gummy exudation from *Acacia Senegal* and other species, Leguminosæ. Northern Africa.

Acacias derived from other species have similar characters and uses.

Acacia is insoluble in alcohol, slowly but completely soluble in 2 parts of water, to a thick, mucilaginous, insipid liquid. This shows an acid reaction to litmus, and is precipitated by alcohol, borax, or metallic salts.

Preparations:

⁂ *Mucilago Acaciæ* (U.S.P., B.P.).—Prepared by washing and dissolving acacia in 2 parts of cold water (U S.P.) [1½ parts, B.P.]. Used in many pharmaceutic preparations as emulsifier, excipient, etc.

⁂ *Syrupus Acaciæ* (U.S.P.).—One part mucilage to 3 parts of syrup.

Tragacantha (U.S.P., B.P.).—*Tragacanth*.—A gummy exudation from *Astragalus gummifer* and other species, Leguminosæ. Western Asia. Swells to a gelatinous mass in water, without dissolving.

Mucilago Tragacanthæ (U.S.P., B P.).—6%.

Glycerinum Tragacanthæ and *Pulvis Tragacanthæ Compositus* (B.P.).

XI. Demulcent Herbs and Other Demulcents.

All these can be taken in decoction, ad libitum. They contain mucilage as their most important ingredient.

Althæa (U.S.P.).—*Marshmallow*.—The root of *Althæa officinalis*, Malvaceæ. Cultivated.

Syrupus Althææ (U.S.P.).—5%.

Ulmus (U.S.P.).—*Slippery Elm Bark*.—The inner bark of *Ulmus fulva*, Urticaceæ. North America.

Mucilago Ulmi (U.S.P.).—6% infusion.

Glycyrrhiza (U.S.P., B.P.).—*Licorice Root*.—See page 119. As demulcent, best as * *Syrupus Glycyrrhizæ*.

Cetraria (U.S P.).—*Iceland Moss*.—See page 116.

Chondrus (U.S P.).—*Irish Moss*.—See page 116.

Sassafras Medulla (U.S.P.).—*Sassafras Pith*.—The pith of *Sassafras variifolium*, Laurineæ. North America.

Mucilago Sassafras Medullæ.—2%.

* *Species Pectorales*, N.F.—(*Breast Tea*.)—Althæa, Coltsfoot Leaves, Glycyrrhiza, Anise, Mullein Flowers, Orris Root.

Gelatinum (B.P.).—An air-dried product of the action of boiling water on gelatinous tissue. Soluble in hot water. Solutions of 2% and above solidify on cooling. Insoluble in alcohol. Also precipitated by carbolic acid; not by dilute solutions of metallic salts.

Ichthyocolla (U.S.P.).—*Isinglass*.—The swimming bladder of *Acipenser Huso* and other species, Sturiones. Caspian and Black Seas. Contains 98% of Gelatin.

* Not official.

The most important preparations are marked ⁂.

(B) SUMMARY OF THERAPEUTICS OF SKIN DISEASES.

I. Peculiarities.—Dermatitis presents much the same general phenomena as inflammation in other situations, modified, of course, by local conditions. The successive stages of typical dermatitis were discussed in Chapter XXVIII, A, but dermatites are characterized by a great variety of forms. These depend, in the first place, on the existence, in the anatomic structure of the skin, of *several layers* of anatomically and physiologically distinct tissues: the dry, dead, impenetrable stratum corneum; the soft, moist, epithelial stratum mucosum; the vascular stratum papillare; the dense stratum reticulare. The character of the inflammation is also modified by the presence of the *glands*, sudorific and sebaceous, which of course differ in every respect from the surrounding skin.

Being devoid of the protection afforded by the stratum corneum, they present a ready means for the entrance of infection or of irritants. The acid character of their secretion also serves to liberate irritating ingredients from otherwise inactive combinations. The character of the secretion itself may be changed, rendering it irritant or otherwise unpleasant. The oily secretion formed by the sebaceous glands is necessary to the healthful state of the stratum corneum, so that diseases of the glands may cause diseases of the surrounding skin by changes in their secretion, as well as by direct continuity. Toxic substances are also frequently excreted through these glands, and give rise to inflammatory phenomena.

In addition to these physical factors in skin diseases, the surface of the body is endowed with a very rich *nerve supply*, both afferent and efferent. The cutaneous vessels seem to be under the special control of the vasomotor center, and changes are induced in them very readily. In this way skin diseases may arise from central causes through trophic disturbances, as in herpes, or more acutely, as in the wheals of urticaria, which are due to an acute circumscribed edema. Irritation of the afferent sensory fibers or endings of the skin is peculiar in causing the sensation of itching rather than pain.

II. The **etiology** of skin diseases is yet in great part imperfectly understood. So far we know as causes:

External irritation—mechanical, chemic, thermal, etc.

Bacterial infection. Other vegetable or animal parasites.

Excretion of irritant poisons.

Nervous, sensory, vasomotor, or other nutritive changes.

But many relations of skin diseases to other conditions, as recognized clinically, cannot be explained by any of the above factors.

III. Treatment.—In default of a real insight into the etiology, the treatment must be merely empirical, but it can be carried out along the same general lines as in other inflammations. It may be systemic or local.

1. The **systemic treatment** is especially useful in chronic skin diseases, the cause of which is especially apt to be obscure. *General hygiene* is of the greatest importance: attention to digestion and the bowels; diet devoid of irritants, or the vasodilators, as alcohol; rest or exercise, etc. The *medicinal treatment* will consist, in the first place, in tonics, avoiding those which contain irritants, as the aromatic bitters. The influence of arsenic on the general circulation, on nutrition, and its special action on the skin, have been discussed in Chapter XXVII. These tonics are applicable to all forms of skin diseases.

There are a few specifics, such as mercury against the cutaneous syphilides, and thyroid against myxedema.

2. The **local treatment** is precisely on the same principles as that of other inflammations in accessible situations. In general, it should be stimulant (irritant) in chronic cases, sedative (emollient) in acute.

The manner of action of emollients is discussed in the preceding section of this chapter.

The most useful *simple irritants*, which are at the same time *antiseptic*, attach themselves to the aromatic series: the various essential oils, especially the empyreumatic products, as Tar, Oil of Cade, etc.; the balsams, Copaiba, Peru, Styrax, etc.; more violent are Resorcin, Pyrogallol, Chrysarobin, Naphtol; Ichthyol acts more deeply, and is especially effective in causing the absorption of inflammatory products.

Astringents are indicated particularly when the stratum corneum is wanting. Zinc Oxid is perhaps the most valuable. If, on the other hand, there is a hypertrophy of the stratum corneum, this can be removed by alkalies, sulphids, or salicylic acid.

The above are more especially useful when the inflammation is circumscribed. If a *more extensive stimulation* is required, this may be given by salt or other baths.

If the *sensory phenomena*—itching, etc.—are more prominent, local anesthetics may be employed, one of the most useful being carbolic acid.

If the inflammation is due to *parasites*, the condition calls for the parasiticides discussed on page 708.

When drugs are to be applied to the skin in circumscribed situations, this is best done by using them in the form of *ointments*, unless these are especially contraindicated, as when the drug is insoluble in oil (alkalies or salts, etc.), or when the oil would cause a spreading of the inflammation, as in ivy-poisoning.

CHAPTER XXXII.

DRUGS ACTING UPON NUTRITION.

(A) DIGESTIVE FERMENTS.

WHEN the importance of ferments (enzymes) in digestion was recognized, the thought lay near at hand that they would be useful in many kinds of digestive disorders. However, much skepticism has arisen in recent years as to the benefits claimed as the result of their internal administration. Attention is called to the fact that many ferments —especially trypsin—are destroyed by the pepsin. It is therefore very doubtful whether any ferment can be given which will act beyond the stomach. As to this organ, physiologists have long since demonstrated that gastric digestion is relatively unimportant. The symptoms of dyspepsia are rather due to irritation than to deficient digestion. And whilst there is no doubt but that the secretion of pepsin may be deficient in certain conditions, it is by no means proved that this is the case in the diseases in which such deficiency is ordinarily assumed. The benefits ascribed to pepsin should perhaps in many cases be credited to the other remedies which are joined to it. However, there can be no doubt that pepsin itself is beneficial in certain cases; and as its administration is neither dangerous nor unpleasant, it may be tried. When the gastric juice is deficient in *acid*, the activity of pepsin will be greatly diminished. The administration of acid by mouth will not always remedy this condition, since it may be too quickly absorbed. In this case *Papain* may be preferred, since it acts in all media.

Unfortunately, the commercial preparations of this ferment differ very greatly in their value, and often do not possess any digestive property. No results whatsoever can be looked for from the administration of the pancreatic ferments.

Whilst the usefulness of ferments on internal administration is therefore a very limited one, the case is quite different with *in vitro* digestion. They are of the greatest value in the *preparation of predigested food.*

Another use to which the proteolytic ferments may be put is the *solution of croupous or diphtheritic membranes* by local application.

Ferments have never been isolated in pure condition, and opinions vary as to their real nature. They are, however, probably related to the proteids. As brought upon the market, they are generally quite impure.

The following are the most important:

I. Proteolytic Ferments.

Pepsinum (U.S.P., B.P.).—*Pepsin.*—Obtained from the mucous membrane of the stomach of the pig (or sheep or calf, B.P.). Capable of digesting not less than 3000 parts of coagulated egg-albumen (U.S.P.) [2500 parts, B.P.] when the test is made according to the official directions.

Various processes are used in its manufacture. The product may be in powder or scales. It is soluble in water, insoluble in alcohol, etc. *Dose:* 0.2 to 1.0 Gm. (3 to 15 grains).

Pepsin will (*practically*) *digest only in an acid medium* (0.4% HCl is the best).

Preparations:

⁂ *Pepsinum Saccharatum* (U.S.P.).—*Saccharated Pepsin.*—Contains 1 part of the above pepsin, triturated with 9 parts of sugar of milk. It should digest 300 times its weight of egg-albumen. *Dose:* 0.3 to 4.0 Gm. (5 to 60 grains). Combined with Bismuth Subnitrate as powder, this is one of the favorite remedies in infantile diarrheas.

**Liquor Pepsini* (N.F.).—Pepsin 4, Hydrochloric Acid 1.2, Glycerin 32, Water to 100. *Dose:* 4 to 8 c.c. (1 to 2 drachms).

⁂ *Liquor Pepsini Aromaticus* (N.F.).—Contains 1.75% Pepsin, 1% of official Hydrochloric Acid (= ⅓% absolute), Aromatics, Glycerin, and Water. (Each fluidrachm = 1 grain of Pepsin.)

⁂ *Glyceritum Pepsini* (N.F., B.P.)—8.5% Pepsin, 1% Hydrochloric Acid, 50% each Glycerin and Water.

**Elixir Pepsini* (N.F.).—1.75%. *Vinum Pepsini* (N.F.).—1.75%.

It is probable that the alcohol in the last two preparations causes a gradual deterioration in the activity of the ferment.

⁂ *Pancreatinum* (U.S.P.).—*Pancreatin.* A mixture of ferments prepared from pigs' pancreas. Occurs as a dry powder, soluble in water. *Dose:* 0.3 to 1.0 Gm. (5 to 15 grains). Digests best in alkaline solution (1% Sodium Carbonate), but also somewhat in a very weakly acid solution (0.1% HCl).

Liquor Pancreatis (B.P.).—2 c.c. should digest 80 c.c. of milk.

* Not official.

The most important preparations are marked ⁂.

**Papain* (*Papoid, Plant Pepsin*).—A proteolytic ferment from the juice of the unripe fruit of *Carica Papaya*. *Dose:* 0.1 to 0.5 Gm. (2 to 8 grains). For solution of false membranes, used in 5% solution. Digests in any reaction of medium.

**Ingluvin*.—The dried and powdered membrane of chicken's craw. Claimed to be especially useful in the vomiting of pregnancy *Dose:* 0.5 Gm., one-half hour after meals, followed by 30 c.c. (1 ounce) of 1% (official) Hydrochloric Acid.

II. Amylolytic Ferments.

Pancreatinum (see above) also possesses an amylolytic ferment.

⁂ *Extractum Malti*.—When prepared at a low temperature, contains diastase. It may be used to artificially digest starchy foods. It is itself very rich in carbohydrates, and may be used as a food. It is said to save proteids, and is also stomachic. Many liquid malt extracts contain alcohol, and exhibit the action of this substance. *Diastase* itself is not used.

(B) SUMMARY OF THE THERAPEUTICS OF DIGESTION.

Notwithstanding the splendid work which has been done of recent years in the investigation of the dyspepsias, the causes of these conditions are still very imperfectly understood, and the treatment is essentially symptomatic. However, if carefully carried out, the removal of the symptoms is generally followed by more permanent improvement. The most important measure in this respect is perhaps a proper *regulation of the diet*. The subject of dietetics cannot be entered into in this treatise, nor can any rules of general applicability be laid down. An intelligent patient can give the best indications as to the diet which is best adapted to his particular case, and if this is adhered to for sufficient time improvement usually results.

Any attempt at a rational therapeutic treatment can only be based upon a thorough physical and chemic examination of the existing conditions; else it cannot be anything but empirical and haphazard, apt to do more mischief than good. When the pathologic state is well understood, we may, from our knowledge of the physiology of digestion and the methods by which this may be modified, arrive at the theoretic indications and the manner in which these should be met. Clinical observations made with all the aids of modern science are as yet hardly sufficiently numerous to bear out these theoretic data.

The **indications** are as follows:

(A) Gastritis, Acute or Chronic.—*1. Removal of the irritant*, whether toxic, undigested food, or toxic products arising from these. These indications are met by emptying the stomach. In acute cases this may be done by *emetics*, or in either acute or chronic cases by *lavage*.

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* Not official.

The most important preparations are marked ⁂.

2. If the cause lies in *fermentation*, the lavage should be carried out in weakly antiseptic and acid solutions. The *antiseptics* must, of course, be devoid of marked toxicity. Boric acid, salicylic acid, or salol are well adapted. The *acidity* should be that of the normal gastric juice, or about 0.2% HCl.

3. Protection of the organs against irritation. This may be done by *demulcents*. Especially in chronic cases, it is best to employ those which are at once nutritive, such as milk or eggs. With irritant poisons mucilage or oil may be more effectual.

4. Physiologic Rest.—This may be secured by using food with the minimum of indigestible residue and the maximum of nutritive value to a given bulk. It should be as free as possible from large particles, and it may be necessary to use it entirely in liquid form. In some cases it will be necessary to have the food largely predigested.

5. In the chronic form a *mild irritation* may be indicated. This may be secured by carbonated waters, by salts, or by the general group of stomachics—bitters, light alcoholic beverages, etc.

(B) **Hypersecretion of mucus** demands *lavage*. This is rendered more efficient if a small quantity of *alkali*, most usually sodium bicarbonate, is added. The latter is frequently beneficial even without lavage. The *astringents* may also be useful, especially bismuth in the form of subnitrate.

(C) **Anacidity** demands *acids*. *Alkalies* tend to cause an increase in the secretion of acid as well as of ferment, and may in this way be useful if the anacidity is functional; they are worthy of trial. *Stomachics* act in the same manner, and are free from the objection of the neutralization of the acid.

Hyperacidity causes irritation, and should be removed by *alkalies*. The irritation may be lessened by the administration of demulcents or of oils.

(D) **Absence of Ferments.**—The ferments were supposed to be lessened in many chronic diseases, as chlorosis, tuberculosis, etc. There is no proof for this belief, and they are generally much less subject to change than the acid-secretion. It is established that they are often deficient in chronic gastritis, in carcinoma, and in certain nervous dyspepsias; whilst they are increased in other cases of the latter and in ulcers. However, it is doubtful whether the ferment action of the stomach is very important.

Deficiency of *pepsin* may be met by the introduction of the artificially prepared ferment. Notwithstanding the doubts which may be entertained as to its theoretic indication, it appears to give clinical results, and can do no harm. *Papain* has the advantage of digesting in all media. The advantages of ingluvin are perhaps doubtful. Pancreatin can do no good, since it is destroyed in the stomach.

The secretion of ferments may be stimulated in a more rational manner by *stomachics or alkalies.*

(E) The symptoms of dyspepsia are as often due to **motor deficiencies** as to faulty chemic digestion. The indications in this condition are met by lavage; small amounts of food taken at frequent but regular intervals; the prevention of fermentation by acids; the application of cold and electricity; the administration of salts or nux vomica.

(F) Many cases of dyspepsia are purely **nervous**; *i. e.*, unconnected with any pathologic alteration. In these cases the education of the patient to greater confidence is of most importance. Of drugs, caffein, nux vomica, and bromids are variously successful.

Some of the clinical symptoms may become sufficiently prominent to require special treatment. *Pain* can be relieved by heat, or if necessary by narcotics; *gas* by sodium bicarbonate; *anorexia* by stomachics; *bad taste* by aromatics (myrrh).

Intestinal digestion seems to require no special aid unless bacterial processes supervene, when a purge will answer the indication. If, however, the intestine is the seat of inflammation, or when excessive food is needed, it may be well to lessen its labor by the administration of predigested foods.

(C) NUTRIENTS.

Another class of diseases in which the digestion needs special attention comprises those in which forced nutrition is indicated. These require care not to overtax the digestive organs, an object which may be secured by the proper selection of the food and by artificial predigestion. The subject of dietetics cannot be entered into here in its hygienic aspects, but only in so far as it relates to therapeutics. The subject of infant feeding is left for special text-books.

The treatment of obesity and diabetes is also studied preferably in connection with these diseases.

In discussing the different kinds of nutrients, we will follow the usual classification into proteids, fats, and carbohydrates; but it must be remembered that all three classes must be administered to secure the required object.

1. **Proteids.**—Of the various **meats**, young lean beef is in most cases the most easily digested. The white meat of fowl enjoys a special reputation, and whilst most clinicians support this, no chemic differences between it and the dark meat have yet been demonstrated. *Cooking* in any form, while it lessens the digestibility *in vitro*, develops aromatic products which act as stomachics. *Raw meat*, finely scraped, is very highly nutritious and easily digested. It is usually flavored with a little scraped onion, salt, etc. Care must be taken, of course, that it does not contain parasites. It has been claimed that dogs fed on raw meat resist tuberculous infection better than ordinary animals.

Of the **concentrated meat preparations**, the ordinary extracts, made after the type of *Liebig's*, possess no nutritive value, and act only as stimulants. **Meat juices** prepared without heat are more digestible than the whole meat, because they are devoid of the fiber; however, they are very expensive.

Opinions have varied as to the value of **predigested foods**, albumoses, etc. It seems certain, however, that if properly prepared they do have a special nutritive value, since they contain a large amount of proteid material and throw less labor on the digestive organs. The principal difficulty in their administration is that the commercial products of "peptones" (which are really albumoses) possess a disagreeable, bitter taste, and patients soon refuse to take them. This taste, which is mainly due to putrefactive changes, can be avoided by having them freshly prepared in the house of the patient by the methods given below. They can then be flavored with the usual condiments, the addition of a little meat extract being especially useful. The so-called "liquid peptone" preparations, etc., as found on the market, contain so small a proportion of proteid that they cannot act as nutrients in the amounts usually taken, but only as stimulants.

The predigested preparations find an important use in rectal alimentation.

General Rules for the Preparation of Predigested Foods of

All Kinds.—The meat should be lean and finely hashed. Starch should be boiled. The mixture is brought to about blood heat, the ferment added, and the heating continued at this temperature for one-half hour (milk), or two or three hours (meat).

Pepsin is the most useful ferment for the digestion of meat; pancreatin is somewhat more active, but carries the digestion to the unutilizable leucin, etc. Pancreatin is especially useful for milk, since it also contains a ferment acting on carbohydrates. The curdling of milk may be accomplished by rennet. Diastase in the form of extract of malt, prepared at a low temperature, is most useful for the digestion of starch.

The *quantity of ferment* to be employed and the *reaction of the medium* are as follows, using the United States Pharmacopœial preparations :

Pancreatin, Milk : For 1 pint take 5 grains pancreatin and 20 grains sodium carbonate.

Rennet, Milk : For 1 pint take ½ drachm Liquor Seriparus, N.F.

Pepsin, Meat : For 1 pound take 3 pints water, 2 drachms pepsin, 1 ounce dilute HCl, U.S.P. Flavor with meat extract.

Eggs present proteids in a very digestible form, especially when soft boiled. They have the disadvantage that they soon become tiresome. **Milk** contains not only proteids, but also carbohydrates and fats. It also quickly becomes tiresome to adults, and, further, it has a tendency to produce constipation. The former objection may be obviated by giving it in different forms, such as curd produced by rennet, as koumiss, etc. The proteid of milk—**cheese**—is very rich in assimilable nitrogen, but it is often not very digestible.

The **proteids of vegetables** are less easily assimilable than those of animal origin. They require very thorough cooking. Legumes are liable to give rise to flatulence and diarrhea, through bacterial decomposition of their carbohydrate constituents.

Gelatin, although not a true proteid, contains a large percentage of nitrogen, and it may replace the proteid constituents of the food to some extent (as usually given, by about 25%), but not entirely. It is easily digested.

2. **Fats.**—Fats are the most extensive source of energy,

and they may to a certain degree save proteids. They are especially useful in conditions of emaciation, such as are found in tuberculosis, etc.

The digestion of fats in large amounts presents considerable difficulty. Since they are practically insoluble, it is evident that their absorption will be largely facilitated by having them in very fine subdivision; in other words by emulsification. This emulsification is very greatly favored by the presence of free fatty acids, which can form soaps with the sodium carbonate of the intestinal fluid; these soaps act as emulsifiers.

The digestibility of the different fats is therefore generally proportionate to the amount of free fatty acid contained in them. This is probably the explanation of the almost specific action of **cod-liver oil.** This oil also contains small quantities of ptomain-alkaloids, as well as some iodin and phosphorus, but in quantities too small to justify us in attributing to them any of the actions. It is best given in the form of emulsion, because in this the fat is already subdivided, and because it makes possible the flavoring of the preparations.

An artificial substitute for cod-liver oil has been made by adding 1 part of oleic acid to 6 parts of olive oil (*lipanin*). This shares some of the qualities, but on the whole is not as efficient. So-called *tasteless preparations* of cod-liver oil, said to contain its valuable alkaloids, must be considered worthless as nutrients.

Emulsions of petroleum have also been introduced as nutrients, but are entirely unabsorbable and without action, except as intestinal emollients.

Butter is also very digestible, since the globules of fat which form it are in a state of fine subdivision. This, of course, does not hold true of butter which has been melted, and which is no more digestible than other melted fats.

The least digestible of fats is the fatty tissue in which the cells are intact, such as bacon, etc. However, a healthy individual is able to digest perfectly moderate amounts of any fat. The differences become important only when very large quantities must be taken, or when the digestion is deranged.

3. **Carbohydrates.**—These are also useful as sources of energy and possibly for the formation of fat. They cannot, however, save proteids as efficiently as the direct addition

of fat to the diet. Carbohydrates may be given in the form of *starch* or *sugar*. Both are for the most part converted into glucose before being absorbed. The digestion presents considerable difficulty in the case of raw starch, so that a thorough boiling is essential. The finer starches (arrowroot, tapioca, sago, salep, etc.) used for invalids possess mainly the advantage of a finer flavor. The starches of the leguminous plants are not so easily digested as those of the cereals. Starches may also be predigested by malting. Such preparations found on the market as "*malted foods*" are superior to glucose or cane-sugar by causing less gastric irritation.

Decoctions made from *Irish and Iceland moss* also serve to some extent as nutrients, but the gums of which they are constituted do not digest very readily. *Glycerin* also aids in saving the proteids to a small extent, but would not be given as food. The rules for *alcohol* have been discussed on page 426.

4. In certain conditions it becomes necessary to avoid alimentation by the mouth entirely. Recourse must then be had to **rectal feeding.** The mucous membrane of the rectum has considerable power of absorption even for undigested foods. This, however, is not sufficient to support the organism for a great length of time, varying with the previous condition of the patient, especially as regards adipose tissue. Proteids and carbohydrates are practically the only forms of food which can be given in this manner to advantage. The food is introduced into the rectum in the form of enemata.

These must be made as non-irritant as possible; *i. e.*, they must not be too concentrated, and must be used in small quantities, of 1 to 3 ounces at each injection. The constituents must of course all be in the liquid form, and it is of considerable advantage to have them predigested.

Subcutaneous feeding—alimentation by subcutaneous injections—has also been attempted. This is impracticable for proteids and carbohydrates, for their injection causes a nephritis if they are used for some time. Nor are they of any use as nutrients, for while they are burned in the organism, they do not seem to save any other constituents, and animals die even more quickly than when simply starved. *Oil*, however, can be very well given by this method; 10 to 100 Gm. per day of olive oil being slowly injected into the subcutaneous tissues with the same technique as is used for the injection of antitoxic serums.

MATERIA MEDICA.

Oleum Morrhuæ (U.S.P., B.P.) (*Oleum Jecoris Aselli*).—*Cod-liver Oil.* —A fixed oil from the fresh livers of *Gadus Morrhua* and other species, Pisces.

Besides the ordinary constituents of animal fats, it contains a large proportion of free fatty acids; it also contains biliary constituents and traces of iodin and phosphorus and ptomains, the quantity of the latter varying with the time that the livers have lain before the extraction of the oil.

Dose: 8 to 15 c.c. (2 to 4 drachms), best given in emulsion.

Starches (see pp. 116 and 117).

Amylum (U.S.P., B.P.).—From the seed of *Zea Mays* (Indian Corn), Gramineæ.

The starches known as arrowroot, sago, etc., have a more delicate flavor, and are often preferred.

(D) GENERAL TONICS AND ALTERATIVES.

These terms are used very loosely. They relate to purely clinical phenomena, without taking into account the underlying action. As therapeutic groups, therefore, they include a very heterogeneous collection of remedies.

Tonics are defined as remedies which improve the general health, vigor, and energy of the patient; *Alteratives*, as those which alter metabolism. The latter are usually employed for the production of tonic effects.

Tonics and Alteratives are found generally useful in all conditions in which there is faulty nutrition. This may arise from faults of diet or digestion; from excessive or insufficient use of tissue; from faulty oxidation or excretion of waste-products; or from other perversions of metabolism not at present understood. Such conditions occur almost invariably in the course of chronic disease or poisoning. In other words, whenever one or more organs are prevented from fulfilling their function in a normal manner, the nutrition of the whole body suffers, and the phenomena of general lassitude, want of energy, nervousness, neurasthenia, etc., make their appearance.

When the underlying cause can be discovered and removed, this will also remove the symptoms. But in many cases this is impossible, and the conditions must be treated symptomatically. Certain tonic measures are then always indicated and of benefit: Diet, attention to the stomach and intestine, stomachics and nutrients, hygiene, exercise, or rest, baths, climate. Certain "nerve-tonics" are also generally useful. These are drugs which increase the irritability of the spinal cord, and hence the reflex tone, which is usually low in these conditions. Stychnin is the most typical of this class.

When the cachexia is more profound,—as in tuberculosis, tumors, anemias, in the " dyscratic diseases,"—these tonics will scarcely be sufficient, although always useful. Recourse is then had to *alteratives.*

The value of this class of drugs was established empirically, and was at first considered more than doubtful, when the critical spirit of rational therapeutics subjected them to scientific inquiry. Direct experiments intended to demonstrate their action upon metabolism gave very inconstant results, nor were the clinical data at all uniform. However, experience speaks so strongly in their favor that modern pharmacologists and clinicians all acknowledge their action.

The inconstant results are not surprising. Indeed, we know much less about their action than is generally supposed. When we stop to consider that even in metabolism-experiments on animals at least three factors are involved, —absorption, metabolism, and excretion,—and that each of these will be modified by a number of side-actions, it will be plain that the results will not be easy to interpret. A consultation of the original literature impresses one with the fact that the increase or decrease of nitrogen excretion noted in most experiments, and quoted as decisive in most text-books on therapeutics, is so small as to fall within the natural variations, and may be purely accidental. Indeed, the number of drugs of whose effect on metabolism we can feel certain is growing less and less. Nor are we any better off in regard to the disturbance of metabolism in the diseases themselves. In such diseases as scurvy, gout, diabetes, phthisis, chlorosis, and carcinoma, where there is undoubtedly marked nutritive derangement, the study of the metabolism by our present methods presents no striking peculiarities. The fact of the matter is, that the examination of the end-products gives us but very little indication of what really occurs in metabolism, and yields but very little insight into what appear to be some of its most important phases. We may conceive, for instance, that the amount of N absorbed and excreted is quite normal, but that in its disassimilation, the molecule fails to pass through some particular stage necessary to the organism.

The pharmacologist may predict that for certain reasons a certain poison is bound to produce *some* modification in tissue change. The clinician may record that it is beneficial in a certain proportion of cachectic disease of a certain type. But as long as the former cannot predict the nature of the change in all its phases, nor the latter explain the nature of the condition which he finds benefited, so long will a rational application of alteratives be impossible. They must be tried empirically in every case, one after the other. Used in this way, they are often very serviceable.

The principal exceptions to this empiricism are the benefits of thyroid in thyroid disease and in obesity; of ovarian substance in post-climacteric conditions; and possibly those of mercury in syphilis.

From a pharmacologic standpoint we may conceive the action of these substances on the cells as being due to:

1. Irritation as molecular foreign bodies (neutral salts, especially iodids; alcohol).
2. Change of reaction of tissues (acids or alkalies).
3. Direct diminution of oxidative changes (P, As) or N metabolism (quinin).
4. Substitution of their own molecules for those of the tissues (alcohol, fats).

The numerous vegetable alteratives are either entirely inactive or owe their action to the presence of bitter or cathartic principles, and are discussed in those groups.

PART III.

PRACTICAL EXERCISES.

CHAPTER XXXIII.

WORK IN CHEMISTRY.

THIS work should be done by every student individually.

LIST OF REAGENTS.

The following will be found convenient on the shelves of the working tables near each student. Others can be given out as needed.

H_2SO_4, conc. C. P.
HCl, conc. C. P.
Alcohol, 95%.
$K_2Cr_2O_7$, saturated (about 3½%).
$Pb(C_2H_3O_2)_2$, 10%.
$Ba(OH)_2$, saturated.
$AgNO_3$, 1%.
KI, 3%.
K. Ferrocyanid, 5%.
K. Ferricyanid, 5%.
$HgCl_2$, 1%.
$BaCl_2$, 10%.
$FeSO_4$, 5%.
$CuSO_4$, 5%.
$HC_2H_3O_2$, 5%.
Picric Acid, saturated.
NaOH, 10%.
NH_3, 5%.
HCl, 5%.
HNO_3, conc. C. P.
I + KI, 1% I.
H_2SO_4, 5%.
Fe_2Cl_6, Tincture.
Ol. Olivæ or Gossypii.

Normal Salt.
Bromin Water.
Glycerin.
Na_2CO_3, 5%.
KI + HgI_2.[1]
$Ca(OH)_2$.
Ether.
Chloroform.
Magnesia Mixture.[2]

Litmus Paper.
NaCl, crystals, powdered.
$MgSO_4$, powdered.
$(NH_4)_2SO_4$, powdered.
Na_2SO_4, powdered.

[1] *Potassio-Mercuric Iodid* (*Mayer's Reagent*):

$HgCl_2$	13.55	Gm.
KI	49.8	Gm.
Water q. s.	1	Liter.

[2] *Magnesia Mixture:*

$MgSO_4$ Crystals	1
NH_4Cl	1
NH_3 (10%)	4
Water	8

EXPERIMENT I.

INCOMPATIBILITIES.

Explain the changes which occur (see pp. 91 to 94).
Unless otherwise stated, use the solutions, and make reactions in a test-tube.

1. Add to a crystal of Chromic Acid in a capsule a small drop of Glycerin: Brown color. Heat: a small explosion or deflagration. Add a few drops of water: Green color. (End-reaction: $14CrO_3 + 3C_3H_8O_3 = 7Cr_2O_3 + 9CO_2 + 12H_2O$.)

2. $K_2Cr_2O_7$ + Alcohol; no change. (There may be a slight precipitate, which redissolves if a little water is added.) + Conc. H_2SO_4. Green color, and evolution of gas.

$$(K_2Cr_2O_7 + H_2SO_4 = 2CrO_3 + K_2SO_4 + H_2O.$$
$$4CrO_3 + C_2H_6O = 2Cr_2O_3 + 2CO_2 + 3H_2O.)$$

3. Conc. HCl + dry $KClO_3$ + heat: Evolution of Chlorin Gas; liquid turns golden or canary color.

$$(2HCl + KClO_3 = KCl + ClO_2 + Cl + H_2O.)$$

4. $FeSO_4$ + (a) NaOH = Green precipitate.
    (b) Na_2CO_3 = Green precipitate.
    (c) K. Oxalate (let stand) = Yellowish-white precipitate.
    (d) Na. Borate (let stand) = Greenish precipitate.
    (e) Na_2HPO_4 = Grayish-white precipitate.
    (f) Tannin = Dark blue.
    (g) Infusion Uvæ Ursi = Dark bluish-green.
    (h) Infusion Cinchona = Dark green.
5. Fe_2Cl_6 + (i) Gelatin = White precipitate.
    (j) Albumin = White precipitate.
    (k) Acacia = Brown gelatinous precipitate.
    (l) Sodium Salicylate = Reddish-purple color.
    (p) Carbolic Acid = Bluish-violet color.
6. $CuSO_4$ + (a) = Blue precipitate.
    (b) = Bluish-white precipitate.
    (j) = Bluish-white precipitate.
7. $Pb(C_2H_3O_2)_2$ + (j) = White precipitate.
    (m) NaCl = White precipitate.
    (n) KBr = White precipitate.
    (o) Na_2SO_4 = White precipitate.
    Tinctura Opii = Brown precipitate.
8. $MgSO_4$ + (a), (b) = White precipitate.
9. $Ca(OH)_2$ + (c), (e) = White precipitate.
10. $HgCl_2$ + (q) $Ca(OH)_2$ = Yellow to brown precipitate.
    (r) $FeSO_4$ + heat = Blackish-brown precipitate.
    (s) KI; when red precipitate forms, add more KI, and it should redissolve.
    (j) = White precipitate.
11. $AgNO_3$ as (7).
12. $\left.\begin{array}{l}H_2O \text{ to Tincture Guaiac} \\ H_2O \text{ to Spirits Camphor}\end{array}\right\} = \text{White precipitate.}$
    H_2O to Tincture Cinchona = Brown precipitate.
13. (1) H_2O_2 + KI (let stand) = Yellowish-brown color.

$$(4H_2O_2 + 3KI = KIO_3 + 2I + 2KOH + 3H_2O.)$$

(2) KI + $KClO_3$ + HCl (heat) = Brownish color.

$$(KI + KClO_3 + 2HCl = 2KCl + ClO_2 + H_2O + I.)$$

14. Saturated solution Quinin Sulphate + (a), (b), (f) = White precipitate.
(t) + Iodin solution (I + KI) = Brown precipitate.
(u) + Picric Acid = Yellow precipitate.
(v) + Pot. Merc. Iodid = White precipitate.

15. 1 : 100 Strychnin Sulph. + saturated KBr (let stand) = Precipitate of crystal needles.

16. Alcohol + (i), (j), (k) = White precipitate.
Alcohol + saturated solution NaCl = White precipitate. Add water. Redissolves.

17. Tannin + Gelatin = Greenish-yellow precipitate.
Chloral + NaOH : Odor of Chloroform.

$$(C_2HCl_3O + NaOH = NaCHO_2 + CHCl_3.)$$

Put up the following prescriptions. Explain the changes which occur.

18. ℞. KClO$_3$ 1
Glycerini 2
Tr. Ferri Chlor. . . . 1
Aquæ 10
If put up without heating, no change will occur, illustrating the possibility of mixing certain explosives in solution.

19. ℞. Ol. Gossyp. 2
Acaciæ Pv. 1
Aquæ 4
Ft. emuls.
Add alcohol: the solution will "crack."
The alcohol will precipitate the acacia, and so break the emulsion.

20. ℞. Ac. Carbol. Liq. . gtt. 20.
Aquæ . . . . . 10 c.c.
Ft. solution.
(How can this be brought into solution?)

21. ℞. Ac. Sulphur. Dil. gtt. 30.
Mist. Cretæ . . 10 c.c.
Evolution of CO$_2$ and precipitation of CaSO$_4$.

22. ℞. Tincturæ Ferri Chlor .
Tincturæ Cinchonæ
Greenish-brown precipitate.

23. ℞. Solution. Quinin. Bisulph.
Solution. Sodii Salicyl.
āā partes æquales.
White precipitate.

24. ℞. Solution. Strych. S.
Solution. Pot. iodid.
White crystalline precipitate.

25. ℞. Bism. Subcarb. . . . 1
Liquor. Pepsini . . . 10
Evolution of CO$_2$.

26. ℞. Solution. HgCl$_2$
Solution. KI
Red precipitate
Tincturæ Cinchonæ.
Brownish precipitate.

27. ℞. Solution. AgNO$_3$
Aquæ Font.
White precipitate on standing, darkening in the light.

28. ℞. Solution. KI
Spirit. Æth. Nitr.
Brown-red color.

29. ℞. NaCl 1
Aquæ 5
Tincturæ Cinchonæ . 5
Brown precipitate.

EXPERIMENT II.

SEARCH FOR ALKALOIDS, GLUCOSIDS, AND SIMILAR PRINCIPLES IN ORGANIC MIXTURES.

(This may be carried on simultaneously with the following experiments.[1])

It is supposed for simplicity that the mass contains but one active substance. If there are several, the method of procedure becomes more complicated. In a regular toxicologic analysis, every extraction is repeated as long as anything goes into solution. For the present purpose, one extraction in each case will suffice. Nor is it necessary to preserve anything but residues A, B, D, and F.

Dilute the mass with water (if tissues, with about two volumes), acidulate *slightly* with tartaric acid, boil for one-half hour on water-bath, strain through muslin, and to the strained liquid add about as much sand as would correspond to the dry matter, and evaporate on water-bath to a paste. Stir residue with two parts of 95 % alcohol. Let stand and filter. The filtrate will contain all the substances which interest us here. It is evaporated (see Supplementary Remarks) to a very thick extract. This extract is treated with 1 % H_2SO_4. Insoluble residue = **A.** The filtrate is shaken with Ether. The ethereal layer = **B.** The acid watery layer = **C.**

A may contain Croton Oil.

B may contain Caffein, Cantharidin, Digitalin, Picrotoxin.

Distil off the ether and reserve to be tested later according to II.

C contains the alkaloids. It is rendered alkaline with excess of 5 % Na_2CO_3, and again shaken with Ether. The ethereal layer = **D**; the aqueous layer = **E.** **D** contains most of the alkaloids. The ether is distilled off, and the alkaloids are tested for according to I. **E** is shaken with Acetic Ether. The ethereal layer = **F,** contains some alkaloids and especially Morphin. It is to be evaporated to

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[1] The following quantities of drugs (or of others, about 5 Gm. of crude drugs, 50 mg. of alkaloids), mixed with 50 Gm. of meat, can be easily identified by this process:

Aconite:	1 Gm.	Picrotoxin:	20 mg.
Belladonna:	3 Gm.	Strychnin:	4 mg.
Cinchona:	2 Gm.	Tea:	2 Gm.
Convallaria:	3 Gm.	Tobacco:	2 Gm.
Digitalis:	3 Gm.	Veratrum Viride:	1 Gm.
Nux Vomica:	1 Gm.		

dryness and tested by I. The aqueous solution should contain no active substance, and is preserved for control.

A = Portion insoluble in water. Contains Croton Oil.

B = Portion soluble in acidified Ether. Contains Glucosids and Caffein.

D = Portion soluble in alkaline Ether. Contains Alkaloids.

F = Portion soluble in Acetic Ether. Contains Morphin.

I. Testing for Alkaloids (to be made when frog-work is completed):

Residues **D** and **F** are each taken up with a little 1% H_2SO_4 and alkaloidal tests applied (*e. g.*, pot. merc. iodid). If an alkaloid is present,[1] it will probably show in both solutions, but it will be easy to tell from the relative amount of precipitate to which solution it belongs. The two residues are then united.

(For physiologic tests frogs are used unless otherwise specified.)

(a) If the precipitate was greatest in F, test for Morphin (Kobert's test, see p. 767).

(b) If the precipitate was greatest in D, test for all the alkaloids. The most important are the following, which may be sought for in the order given (the acidulated solution being first neutralized until a precipitate just begins to appear):

Atropin (Eye, Heart, Chemic).
Strychnin (Chemic, Tetanus).
Aconitin (Heart).

Physostigmin (Reddening of Solution; Chemic, Eye).
Nicotin (Heart, Paralysis and Twitchings).
Veratrin (Chemic, Muscle, Heart).

Quinin (Chemic).
Cocain (Chemic, Frog's Foot).

(The same frog may be used in testing for those alkaloids which are joined by brackets.)

II. If no Alkaloid is Present:

(a) Test **A** for Croton Oil (inflammation of rabbit's ear); if none is found,

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[1] The physiologic tests for the suspected substances should be tried even if the general alkaloidal tests fail, since the former are usually more delicate.

(b) **Test B** for Cantharidin (Inflammation of Rabbit's Ear).
Picrotoxin (Convulsions).
Digitalis (Heart).
Caffein (Muscle).

Supplementary Remarks.—All evaporations must be done on water-bath (in actual practice at the lowest possible temperature); Ether must be distilled on water-bath with smallest possible flame—not evaporated in open vessels. In making extractions it is always better to let stand ten or fifteen minutes, with frequent shaking.

EXPERIMENT III.

TESTS FOR ALKALOIDS AND SOME OTHER IMPORTANT ORGANIC SUBSTANCES.

1. **General Tests for Alkaloids.**—Place on slides a few drops of 1 : 1000 acidulated solutions of quinin bisulphate and mix with a drop of the following:

(a) Phosphomolybdic Acid [1] = Amorphous white precipitate.
(b) Phosphotungstic Acid [2] = " " "
(c) Pot. Merc. Iodid = " " "
(d) Iodin in KI = " reddish "
(e) Picric Acid = " yellow "
(f) Tannin (1%) = " white "
(g) Gold Chlorid (1%) = " yellow "

The above give similar reactions with most other alkaloids. Some possess characteristic crystalline form.

2. **Lassaigne's Test for Nitrogen.** — Place a knife-pointful of dry quinin sulphate in a dry test-tube. Take a piece of metallic Na, size of small pea, dry with blotting-paper, and add to quinin. Heat red-hot and plunge into beaker with a little water. Filter. Add a few drops $FeSO_4$. Let stand five minutes. Acidulate with conc. HCl and heat: Color or precipitate of Prussian Blue.

3. **Strychnin.**—Evaporate a few drops of 1 : 300 alcoholic solution of strychnin placed on slides and add

(a) a drop of conc. HNO_3; heat gently: With most samples a yellow color develops, due to Brucin.

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[1] *Phosphomolybdic Acid:* To a strong solution of ammonium molybdate add HNO_3 and Na_2HPO_4 to complete precipitation; let stand twenty-four hours, wash by decantation, and dissolve the precipitate by the addition of sufficient NaOH. Evaporate to dryness; calcine until no more NH_3 is given off. Cool and dissolve in water with the addition of sufficient HNO_3.

[2] *Phosphotungstic Acid:* A 10% solution in 4% HCl.

(b) a drop of conc. H_2SO_4 : No change ; then a small crystal $K_2Cr_2O_7$. Play of colors through blue, violet, red.

(c) to 1 : 500 aqueous solution, a drop of conc. $K_2Cr_2O_7$ solution. Let stand and examine the crystals microscopically.

4. To some powdered **Nux Vomica** add a drop of conc. HNO_3 : Orange color, due to Brucin.

5. **Caffein.**—Evaporate a few drops of saturated solution Caffein Citrate in a capsule with a drop of HNO_3 : A yellow residue remains. Let NH_3 vapors plays on this : Purple color (Murexid Reaction).

6. **Morphin.**—1 : 500 alcoholic solution. Evaporate a few drops on slides. Add to

(a) Drop conc. HNO_3 and heat : Yellow-brown color.

(b) Heat a few drops in test-tube on water-bath with a drop of conc. H_2SO_4 for one-half hour : Violet color. Add a drop of 1 : 4 HNO_3 : Cherry red (Huseman's reaction).

(c) To a few drops of 2% aqueous solution in a test-tube add a drop of Fe_2Cl_6 : Blue color.

(d) To a few drops of 2% aqueous solution in a test-tube add about 2 c.c. conc. HCl and a few drops of conc. H_2SO_4. Boil in water-bath for one-half hour : Leaves red oily liquid. Neutralize with Na_2CO_3 (solution) and add a drop of alcoholic Iodin : Emerald color. Shake with ether : This takes violet color (Pellagri's reaction).

(e) (Kobert) Evaporate a few drops of the solution and add to residue a drop of Kobert's reagent (conc. H_2SO_4, 100 c.c. ; 40% Formalin, 5 c.c.) : Play of colors from purple-red to violet-blue.

7. **Codein.**—Evaporate 20 drops of 1 : 1000 solution on porcelain, add some conc. H_2SO_4 : Faint greenish, then violet color. Add a drop of conc. HNO_3 : Plays from yellow to purple.

8. **Opium** (*i. e.*, **Meconic Acid**).—Add a few drops of Fe_2Cl_6 to some ten times diluted Laudanum : Red color, not bleached by $HgCl_2$.

9. **Atropin.**—Evaporate 10 drops of 1 : 100 alcoholic solution in test-tube. Add 10 drops of conc. H_2SO_4, and heat until it becomes brown ; then add 2 volumes of water : Characteristic odor, resembling tuberose, strengthened by $KMnO_4$.

10. **Cocain.**—(a) Evaporate 30 drops of 1% alcoholic solution in test-tube. Add 2 drops conc. H_2SO_4. Warm

in water-bath. An aromatic odor of benzoic acid is developed, and crystals of this substance may form along the sides of the test-tube.

(b) To a little of 1 : 1000 aqueous solution add a drop of Fe_2Cl_6: Yellow color, becoming orange on boiling and changing back to yellow on adding HCl.

11. **Physostigmin.** — (Notice pinkish color.) (a) To 1 : 1000 aqueous solution add 1 drop of NaOH: Red, becomes green on heating, and returns to red on cooling. Add Sulphurous Acid: Again colorless.

(b) Evaporate some solution with a few drops of NH_3: Red color, leaving dry blue residue. Add water: Blue solution. Add Acetic Acid: Violet in transmitted, coppered fluorescent in reflected light.

12. **Apomorphin.**—(Notice greenish color.) (a) Evaporate a few drops of 1 : 1000 alcoholic solution. Add a drop of conc. HNO_3: Blood-red color.

(b) To a few drops of 1 : 500 aqueous solution add 5 drops of Na_2CO_3 and 1 drop of alcoholic iodin: Emerald color. Shake with ether: The latter becomes violet.

13. **Veratrin.**—(a) Evaporate a few drops of 1 : 1000 solution on slide. Add a drop of conc. H_2SO_4. Let stand. Note play of colors, from green through brown and red to yellow.

(b) Repeat this test in a test-tube and observe colors spectroscopically, diluting with conc. H_2SO_4 if necessary. (Bands in red, green, and indigo.)

(c) Evaporate a few drops on slide. Add trace of cane-sugar and a drop of H_2SO_4: Yellow, green, blue, violet color (Weppen).

(d) Evaporate a few drops. Add conc. HCl: Red color.

14. **Quinin.**—(a) Notice fluorescence in saturated solution Quinin Sulph., best seen by drawing the solution into a narrow glass tube. This is increased by acids, diminished by NaCl.

(b) Thalleioquin Reaction: To a little saturated solution of Quinin Sulph. add 2 drops Bromin Water and then cautiously an excess of NH_3. An emerald color results, which is changed to red by HCl. (If a very small quantity of ammonia is used, the color may be magenta.)

(c) To a drop of saturated alcoholic solution of Quinin Sulph. on a slide add a drop of alcoholic solution of Iodin:

Green crystalline precipitate (Herapathite). Examine microscopically: Presents appearance of micrococci.

15. **Picrotoxin.**—Evaporate 5 drops of 1 : 100 alcoholic solution, mix residue with equal amount of KNO_3 and small drop conc. H_2SO_4. Then add excess of NaOH: Transitory red color.

16. **Digitalin.**—(a) Evaporate 6 drops 1 : 100 alcoholic solution with a drop of conc. H_2SO_4 and heat carefully: Reddish-brown color. Expose to Br vapor: Violet to cherry color.

(b) Evaporate 5 drops and add a drop of Fe_2Cl_6 + equal volume conc. H_2SO_4 without mixing: Carmine to violet zone, changing to indigo.

17 and 18. **Pyridin and Quinolin.**—On the 1 % aqueous solutions try some of the general alkaloidal tests, as **1** (c) (d) (f): Gives the same results.

19. **Santonin.**—To a little 1 % alcoholic solution in test-tube add a small piece KOH and warm: Cherry-colored liquid.

20. **Antipyrin.**—(a) To 10% aqueous solution add a few drops conc. yellow HNO_3: Green, then red.

(b) To 10% aqueous solution add a few drops conc. Fe_2Cl_6: Deep red solution; + H_2SO_4: Light yellow.

(c) To 10% aqueous solution add some Spiritus Ætheris Nitrosi: Slow development of green color and precipitate.

21. **Acetanilid.**—(a) Heat some of the powder with NaOH solution: Dissolves, with odor of anilin; add a few drops $CHCl_3$ and heat again: Odor of phenylcarbylamin (resembles witch-hazel).

(b) Boil with conc. HCl, add equal volume 5% C_6H_6O and equal volume calx chlorata: Red turbid fluid. Supersaturate with NH_3: Deep blue.

(c) Rub together equal volumes of Acetanilid and $NaNO_2$ and add some conc. H_2SO_4: Orange liquid.

22. **Phenacetin.**—Gives (a) and (b), as in 21. These need not be repeated. With (c) it gives a black violet color, later passing into green.

23. **Resorcin.**—To a trace add some NaOH and $CHCl_3$: Pink color.

24. **Anilin.**—To some 1 : 500 solution Anilin Chlorid, add:

(a) Some solution calx chlorata: Violet, changing to dirty red.

(b) Some bromin water: Flesh-colored precipitate, later grayish-green.

(c) Some Millon's reagent[1] and heat: Pink color or precipitate.

(d) A matchstick: Becomes yellow to orange.

(e) To some dry anilin chlorin add some $CHCl_3$ and NaOH: Odor of phenylcarbylamin.

25. **Carbolic Acid.**—Use 3 : 1000 Phenol.

(a) Add Fe_2Cl_6: Blue-violet color.

(b) Add bromin water: Yellow precipitate. Let stand and examine microscopically: Needle-shaped crystal.

(c) Add Millon's reagent and heat: Blood-red color or precipitate.

26. **Salicylic Acid.**—(a) To 1% Sod. Salicylate add Fe_2Cl_6: Red-violet color.

(b) To dry Sod. Salicylate add equal parts alcohol and conc. H_2SO_4: Odor of ethyl salicylate.

27. **Benzoic Acid.**—(Make test as in 26, using 1% Sod. Benzoate.)

(a) Brownish-pink precipitate.

(b) Odor of ethyl benzoate.

28. **Salol.**—(a) 1 : 100 alcoholic solution + Fe_2Cl_6: Red-violet color.

(b) Dry crystals + NaOH; heat: Dissolves. Add conc. HCl: Crystalline precipitate of salicylic acid and odor of phenol.

29. **Tannin.**—(a) Add drop of Fe_2Cl_6: Green-blue-black color. Dilute until it is transparent. Add a few drops of NaOH: Garnet color. Add cautiously an excess of H_2SO_4: Greenish-red; with more, greenish-yellow.

(b) Add some $Pb(C_2H_3O_2)_2$: Large white precipitate. Add NaOH and shake: Pink.

(c) Add some NaOH: Reddish-brown color.

(d) Precipitation with alkaloids, proteids, and gelatin have already been studied in Exp. I.

30. **Formates.**—(a) To 1% Sod. Formate add drop of Fe_2Cl_6 and heat: Deep red color.

(b) To dry crystals add 15 drops of alcohol and 20 drops conc. H_2SO_4; heat: Characteristic odor of ethyl formate.

31. **Acetates.**—(a) (as in 30): Same result. (b) (as in 30): Odor of acetic ether.

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[1] *Millon's Reagent:* Dissolve metallic mercury in an equal weight of conc. HNO_3, in the cold; then add an equal volume of water.

32. Oxalates.—(a) (as in 30): Precipitate, but no color. (b) Add $CaCl_2$: Precipitate.

33. Hydrocyanic Acid.—(a) Notice odor.

(b) Impregnate some filter-paper with freshly prepared Tincture Guaiac, let dry, then pour on some very diluted $CuSO_4$; expose this to the vapor of some 1 : 1000 HCN: Deep blue color.

(c) Add to 1 : 1000 solution some $FeSO_4$ and Fe_2Cl_6 and a few drops of NaOH; boil, let stand a few minutes, acidulate with conc. HCl, and heat: Green to blue color, or precipitate of Berlin blue.

34. Alcohol.—(Use 5% solution.)

(a) Add some $K_2Cr_2O_7$ and dilute H_2SO_4 and warm: Green color and odor of aldehyd or acetic acid.

(b) Add some NaOH and Iodin solution; heat gently: Odor of iodoform; a precipitate of this substance may be seen.

35. Chloroform and Chloral: Add some NaOH and a trace of resorcin: Pink color.

36. Formaldehyd: (Use freshly made 1 : 5000 absolute. These tests may be used for formalin in milk.)

(a) *Hehner's Test:* To about an inch of conc. H_2SO_4 in test-tube add few drops of Fe_2Cl_6 and mix; pour on formalin solution without mixing: Violet color, disappearing again very quickly.

(b) *Liebermann's Test:* Mix some of the formalin solution with a drop of 5% Phenol solution and pour cautiously, without mixing, on some conc. H_2SO_4 in test-tube: Crimson zone.

37. Saponin: To a trace of dry saponin on porcelain add 2 drops of conc. H_2SO_4: Canary color. Add trace of water: Gradual development of purple color, which bleaches after some hours.

EXPERIMENT IV.

Test some submitted unknown samples for the substances prescribed.

EXPERIMENT V.

EFFECT OF DRUGS ON FERMENT ACTION.

(Each student will be assigned one experiment in this series.)

Put in each test-tube the following:

1. For Saliva: 1 inch boiled starch (2%).
1 inch 1% Na_2CO_3.
½ inch saliva.
2½ inches Reagents 1 to 15 (see page 773).

2. For Pepsin: 2 inches 1% HCl.
½ inch Gastric Extract.
2½ inches Reagents 1 to 15 (see below).
Small piece of Carmin-Fibrin.

3. For Trypsin: 2 inches 2½% Na_2CO_3.
½ inch Pancreatic Extract.
2½ inches Reagents 1 to 15 (see below).
Small piece of plain Fibrin.

Shake and set in water-bath 40° C. for one hour, then compare the amount of digestion in the different tubes as follows (report in order of digestion):

1. *Saliva:* Add to each tube an equal volume of 10% NaOH and set them in a water-bath, heat and keep boiling for two minutes. The depth of color will correspond to the amount of digestion.

2. *Pepsin:* The depth of color will correspond to the amount of digestion.

3. *Pancreatin:* Add to each tube an inch of NaOH (10%) and then drop by drop a very diluted $CuSO_4$ solution, until the pink just begins to pass into blue. The depth of the pink color will correspond to the amount of digestion.

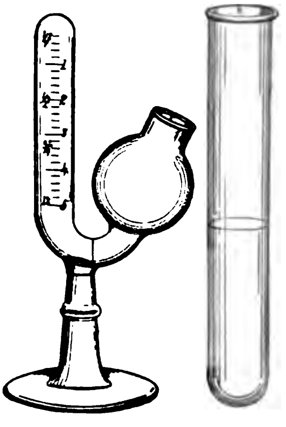

Fig. 85.—Fermentation tube.

4. Yeast: Fill a test-tube with equal volumes of reagent and 5% glucose, and add a small piece of yeast. Shake and introduce into a saccharimeter (Fig. 85) and let stand two hours at 35° C. The amount of action will correspond to the amount of gas evolved. Use water and any five of the reagents.

REAGENTS FOR 1, 2, 3, AND 4.

(It must be remembered that in the finished liquid, the strength will only be half that named below.)

1. Water.
2. Quinin bisulphate, 1%.
3. Quinin bisulphate, 2%.
4. Carbolic Acid, 1%.
5. Carbolic Acid, 5%.
6. Saturated Aqueous Solution of Salicylic Acid.
7. " " " " Benzoic Acid.
8. " " " " Salol.
9. " " " " Boric Acid.
10. Alum, 5%.

[1]11. Formaldehyd, 2% absolute.
[1]12. Alcohol, 50%.
[1]13. Alcohol, 10%.
14. $HgCl_2$, 2 : 1000.
15. $HgCl_2$, 2 : 100,000.

5. **Oxidizing Ferments:** Put in each of five test-tubes 1 inch of Reagents, 1 inch potato pulp, 20 drops Tincture Guaiac, and ¼ inch H_2O_2. Note the time required for the appearance of a distinct blue color, and the depth of color at the end of an hour. Make report, arranging them by amount of oxidation.

Reagents: (a) Water.
(b) 10% Carbolic Acid.
(c) 1% Caffein.
(d) 2% Quinin bisulphate.
(e) 2 : 10,000 $HgCl_2$.

EXPERIMENT VI.

EFFECT OF DRUGS ON RED CORPUSCLES.

Put 2 drops of defibrinated blood in each of 6 perfectly clean test-tubes and add to

(a) 5 c.c. Normal Salt (0.9%).
(b) " 0.01% Digitonin in Normal Salt.
(c) " 2% Na_2CO_3.
(d) " Normal Salt (0.9%) and 20 drops of Ether.
(e) " 0.01% Crude Saponin in Normal Salt.
(f) " Distilled Water.

Shake and let stand one-half hour. Note depth of color of supernatant liquid and report in order of solution of hemoglobin (or inversely to turbidity). Examine some of the sediment microscopically, and note size, shape, and color of the corpuscles. Crystals of hemoglobin may sometimes be seen.

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[1] Stopper the test-tube.

EXPERIMENT VII.

FORMATION OF METHEMOGLOBIN (FIG. 71, p. 470).

Make a solution of three parts of defibrinated blood[1] in 100 parts of water. Put portions of about 15 c.c. in test-tubes, add reagents, and note changes in color and spectrum at once. If none appear, place in a water-bath at 40° C. and observe every half hour.

1. 25 drops saturated $KClO_3$.
2. " " 5% Pot. ferricyanid. When band of met-hemoglobin is well marked, add one drop 2% HCN and note band of Cyan-methemoglobin (resembles reduced).
3. " " 10% $NaNO_2$.
4. " " $KMnO_4$.
5. " " Phenylhydrazin.
6. " " 10% Pyrogallol (Methemoglobin spectrum and precipitate of Hemogallol).

EXPERIMENT VIII.

ACTION OF CHEMIC CORROSIVES. (SEE p. 653.)

1. Precipitation (see p. 654): To defibrinated blood and to solutions of Egg-albumen and Gelatin add:

1. Mercuric Chlorid.
2. Silver Nitrate.
3. Cupric Sulphate.
4. Ferric Chlorid.
5. Lead Acetate.
6. Concentrated H_2SO_4.
7. " HCl.
8. " HNO_3.
9. " NaOH.
10. Carbolic Acid.
11. Alcohol.

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[1] Dog's blood contains on an average 15% of hemoglobin; beef's blood, 10%.

If there is any precipitate, note whether it will dissolve on the addition of water.

2. **Corrosion of Skin** (see p. 659): Place bits of fresh skin in test-tubes containing reagents 6, 7, 8, 9, and 10, leave for some time, rinse in water, and note character of stain, consistency, etc., on epithelial surface.

3. **Corrosion of Mucous Membrane:** With glass rod place drops of above on freshly excised mucous membrane and note character of stain and corrosion.

4. **Corrosion of Muscle:** Place bits of muscle in the reagents, leave some time and examine.

5. **Coagulation of Muscle:** Tease some fresh frog's muscle in normal salt, add the reagents (also add 1 % Caffein), and examine microscopically (low power).

EXPERIMENT IX.

Each student should try on himself[1] and report the effect of:

Aconite:	Two minims of Tincture on tongue.	These are best used in tablet form.
Atropin:	$\frac{1}{60}$ grain.	
Pilocarpin:	$\frac{1}{20}$ grain.	
Digitalis:	5 minims.	
Amyl Nitrite:	3 minims by inhalation: Quickening of pulse and area of flushing.	
Strychnin:	Limit of taste (1 : 50,000).	
Veratrin:	Snuff a very little of a mixture of one part of Veratrin and 500 parts of starch.	
Soap-bark:	Taste. Smell. Add 25 drops of tincture to about an inch of cotton-seed oil. Shake. Add an inch of water and shake. Emulsion. Add Alcohol: remains emulsified.	

Note difference in taste of 1 % solution of *Citric Acid* in water and in starch paste.

Note difference in sweetness of acid and alkaline fluid extract of *Licorice.*

Note difference in taste of a plain solution of quinin and some to which *Yerba Santa* has been added. (Mix 10 c.c. fluid extract with 100 c.c. 1 : 1000 Quinin sulphate.)

Determine comparative sweetness of solutions of Cane-sugar and *Saccharin*, diluting one or the other until they are equally sweet. (Start with 1 : 50 Cane-sugar and 1 : 5000 Saccharin.)

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[1] To make these observations of any value, the student must be careful to do them at such a time that they may not be vitiated by the effects of taking food or exercise, etc.

CHAPTER XXXIV.

INTRODUCTION TO EXPERIMENTS ON ANIMALS.

A SHORT description of the simplest forms of apparatus and operations required for performing the following exercises may be useful for those who have had no experience in this kind of work.

I. APPARATUS.

1. A small **induction coil** is needed. Figure 86 gives an illustration of a simple and effective form. If the *tetanizing current* is required, the binding screws *a* and *b* are connected with the battery, the primary key *Kp* being closed whenever the current is to be used. For *single make and break shocks*, the battery is connected with *a* and *c*, and make and break are made by pushing down or releasing *Kp*.

i is the interrupter which produces the *tetanizing current* if the battery is connected with *a* and *b*. *p* is the primary coil which surrounds a bundle of soft iron wire. The latter serves at the same time as a magnet for the interrupter. The secondary coil *S* ends in two binding screws *s′s′*, to which the *electrodes* are attached. If these are to be used on the nerve, they are best made from heavy insulated wire to which short pins are soldered, the ends being inclosed in glass tubing and bound together. For direct stimulation of the muscle, however, a better arrangement is to connect *s′* with the muscle by means of very fine insulated wires the bared ends of which are thrust directly through the muscle.

To produce a *single break shock*, *s′* is connected with the binding screws of another key, *Ks*. The electrodes (*c*, *e*) are connected with the same binding post. (See Fig. 86.) When *Ks* is closed, the secondary current is short-circuited. To send a single break shock into the muscle: With the finger close *Ks*, then *Kp*, then open *Ks*. When *Kp* is now opened, a single break shock will be thrown into the muscle.

The rail on which the secondary coil slides should be provided with a centimeter scale to enable one to reproduce the same strength of current. In *testing the excitability* of a preparation, the secondary coil is pushed away from the primary as long as the muscle shows any visible contraction. Single shocks are best for this purpose.

2. Almost any form of **battery** can be employed as a source of current. For ordinary work the dry cells are the most convenient, but do not give a very constant current. When the latter is essential, a Daniel cell is the most useful form.

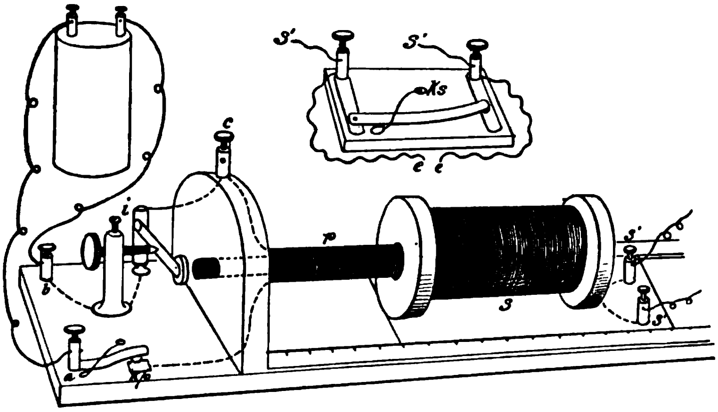

Fig. 86.—Induction coil. (For description, see p. 776.)

3. **Mercury manometers** for use in measuring and recording the arterial pressure are made by bending a piece of glass tubing (as Fig. 87; No. 9 for dogs, 7 for rabbits) into the shape shown in figure 95, *m*. The height of this apparatus may be about 10 inches. It is fastened on a small board which will allow of holding it in a clamp. A millimeter scale should be placed on this board, and the readings may be taken from this directly (always measuring the difference between the two limbs). For taking tracings a small float fitting rather loosely into the straight tube is made of glass or hard rubber, and a long pin (knitting-needle or glass rod drawn out) is fixed in this. This bears

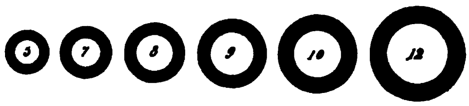

Fig. 87.—Sizes of glass tubing.

on its upper end a flat piece of cork, to which some parchment paper may be fixed by sealing-wax, as a writing-point.

4. As a **vein manometer**, a right-angled glass tube, size 8, can be used, the upright limb about 20 inches long, and provided with a centimeter scale; the short horizontal piece to be connected with the vein. The tube is filled almost full with water before being attached, and after every observation a little water should be run into it with a pipette to make sure that there has been no clotting since the last observation.

5. These manometers, as well as the injection apparatus, are connected with the vessels by means of **cannulæ** inserted into the latter. These can be readily drawn out of glass tubing. The end must be somewhat enlarged and cut off obliquely (Fig. 88).

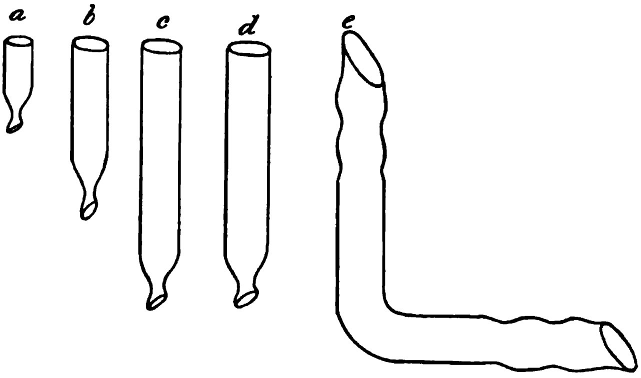

Fig. 88.—Cannulæ.

a is for use in the frog's heart; *b* for rabbit's carotid or dog's femoral artery; *c* for dog's carotid artery or femoral vein; *d* for dog's external jugular; *e* gives the shape of tracheal cannulæ. One end is best made somewhat smaller than the other, so that the same cannula may serve for somewhat different sizes of trachea. Tubing 5 and 8 is most useful for rabbits; 9, 10, and 12 for dogs.

6. **Hypodermic injections** into mammals are made with antitoxin syringes, using especially large ("aspirator") needles. For **intravenous injection** a cannula in the vein is connected with a burette containing the injection fluid. A small syringe may be used instead, but is less satisfactory.

If the solution is to be **injected under pressure,** the injection apparatus illustrated in figure 48 (p. 248) is to be used.

7. For taking the **tracings** a cylinder ("drum"), revolved by clock-work or motor, is employed. A sheet of glazed paper is wound around this drum and the edges are trimmed. The paper is covered with soot by rapidly revolving the cylinder in a fish-tail flame. The coating should not be very heavy. As writing-points, one may use slips of parchment paper, 3 cm. long and 1 cm. wide, tapering to a fine point, attached to the levers by sealing-wax. When a tracing has been taken, it may be fixed permanently by passing the paper, after cutting it from the drum, through a saturated solution of orange shellac in alcohol, and allowing it to dry. Any notes, etc., must be written on the tracing before it is varnished.

II. OPERATIONS ON FROGS.

To pith a frog, it is held in the left hand and the head bent slightly forward with the thumb. If the finger-nail is passed lightly along the spine a slight depression will be felt back of the head. A narrow-bladed knife is thrust in here, and the brain or cord can then be destroyed by pushing in a stiff wire. When this is withdrawn, the wound should be stopped with a short piece of pointed match to avoid bleeding.

To destroy the brain only, a line is drawn joining the posterior edge of the tympanic membranes, and the skull opened in front of this line and the brain destroyed.

To make a muscle-nerve preparation, the frog is pithed through brain and cord. It is then held up by the legs so that the anterior part of the body falls down. The scissors are thrust through the body a little anterior to the angle and the whole body is cut off. By grasping the skin with a cloth it can be readily removed from the legs. The two legs are then cut apart just in the median line. The iliac bones (the two bones at the sides) are cut away. Each portion is then turned with the posterior surface upward, and the muscles of the thigh are pulled apart with the fingers. The sciatic nerve will be seen lying at the bottom of the groove. It is carefully dissected out with a few cuts of the scissors, from the spinal canal to which it is attached, to the knee. The thigh is then cut off so as to leave a short piece of the femur attached to the knee. A blade of the scissors is then thrust under the tendo Achillis, and pushed as far as possible toward the toes. The tendon is then cut off at this point. The tibial bone is also divided close to the knee. In this way a preparation is formed consisting of a small piece of bone of the spinal column attached to the sciatic nerve, a bit of the femur, the gastrocnemius muscle, and the tendo Achillis. These preparations must be carefully kept from drying by wrapping in filter-paper soaked in normal saline solution.

To take a **simple tracing of a muscular contraction,** both ends of the muscle are tied to little hooks which are inserted into the holes in the lever and the support of figure 89 (p. 781). The limb *a* is lowered until the muscle is brought to the proper stretch and fixed by the set screw. A weight should be hung on the other limb of the lever at an equal distance from the fulcrum. The nerve may be placed on the electrodes, or if direct stimulation is required, the wires are inserted into the muscle. The end of the writing lever, which is best made of a straw about 5 inches long, is fixed to the metal with sealing-wax. The straw should bear a writing-point of parchment paper. By adjusting this on a rapidly revolving drum a tracing of the muscular contraction can be taken. The writing-point of the lever should be bent somewhat toward the drum and the lever should be placed as much as possible at a tangent. If it is required to subject the muscle to the influence of reagents or to heat or cold, this may be done by lowering the whole apparatus into a beaker filled with the solution.

To **expose the heart,** the frog is pithed, brain only. An incision is then made in the median line through the abdomen and the upper part of the body. The cartilage between the arms is divided and the arms are pulled well apart and fixed to a small board with pins. The heart can then be seen beating. If it is to be treated with reagents, the pericardium should be opened. The frog's heart will be seen to consist of two auricles and a single ventricle. From the ventricle arises a small, whitish bulbus aortæ, and from this the two aortæ. If the heart is turned up, it will be seen that the auricles are continued into the sinus venosus. A white line marks the junction of the two. The stimulation of this line stimulates the vagus ganglia. If the heart is to be handled considerably, it will be convenient to place a silk ligature around the frenum, the delicate fibrous band attaching the lower surface of the heart to the pericardium. This can then be divided and the heart turned by the ligature.

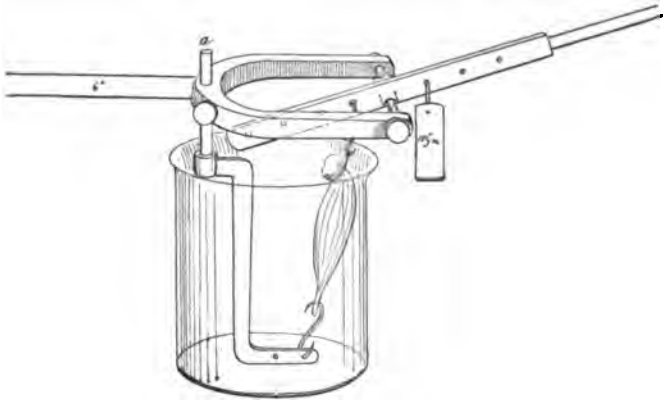

Fig. 89.—Muscle lever.

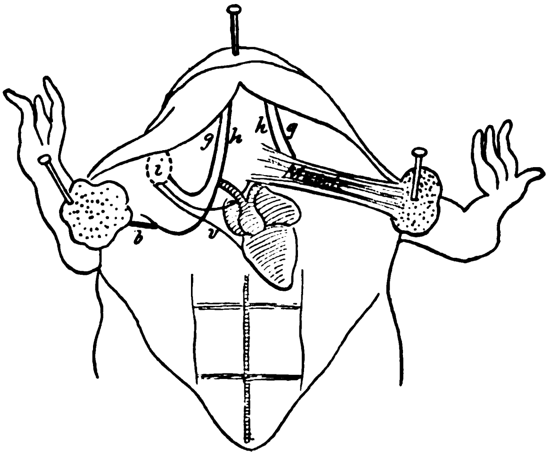

Fig. 90.—Dissection of vagus: *v*, Vagus nerve; *h*, hypoglossal nerve; *g*, glossopharyngeal nerve; *b*, brachial plexus; *j*, jaw.

If drugs are to be applied, this is conveniently done with a pipette or a camel's-hair pencil.

Heart tracings are, as a rule, unsatisfactory. If it is wished to take them, the muscle lever can be used by attaching a small piece of cork to the lever in the place of the weight, and resting this cork on the exposed heart.

The **vagus trunk** comes to the surface at about the angle of the jaw, in company with the glossopharyngeal and hypoglossal nerves, lying between the two. By exposing this area the vagus can easily be seen passing to the heart (Fig. 90). It may be dissected out and placed on a ligature for stimulation, but frequently it suffices to stimulate it *in situ*.

III. OPERATIONS ON MAMMALS.

To give a drug by the stomach, a stout, stiff male catheter is attached to a small bulb of the kind used on the Williams apparatus and holding about 50 c.c.. The mouth of the animal is held open with a stick and the moistened catheter is passed well back, when no difficulty will be found in making it enter the esophagus. Care must be taken not to push it into the trachea, and it is well to note that the animal does not breathe through the catheter. The solution is then poured into the bulb. If it does not flow readily, it can be quickened by blowing.

Anesthesia.—Operative work is to be done only on completely *anesthetized animals*. Dogs should be given 0.02 Gm. per Kg. of morphin hypodermically half an hour before using. They are then anesthetized by inhaling any of the liquid anesthetics.

In the case of rabbits, the anesthetic, dissolved in water, is best given through a catheter into the rectum. The dose per Kg. is: of Chloral, 0.3 Gm.; Urethane, 0.75 Gm. About fifteen to twenty minutes are allowed for the development of the narcosis. If this is incomplete, it may be supplemented by the inhalation of ether. Chloroform is rather too dangerous for these animals.

Volatile anesthetics may be given to animals on cotton covered with a towel, taking care to cover the whole mouth of the animal. When long-continued anesthesia is required and the trachea is to be opened in the experiment, the anesthetic is continued through the tracheal cannula. An arrangement as in figure 91 is very useful for this purpose. It consists of a Woulf's bottle containing the anesthetic. The tracheal cannula is connected with one mouth of the bottle and prevented from falling in by a screw-cock. The other mouth bears another tube, which can be narrowed by another screw-cock. By adjusting these cocks the amount of anesthetics can be increased or diminished. In the illustration is shown the manner of connecting this with Marey's tambour for taking **respiratory tracings.**

Another method of taking respiratory tracings through the trachea is by connecting it with the respiration bottle, shown in figure 92. In this case the connection of the trachea with the tambour can be made perfectly tight and the exact form of the curve recorded. But dyspnea results quite quickly if the vent is closed.

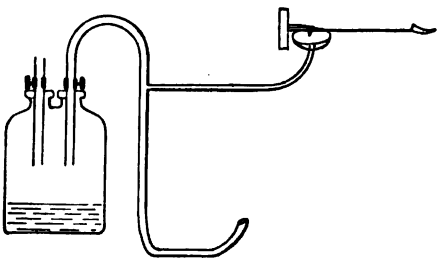
Fig. 91.—Woulf's bottle for giving anesthetic (also arranged for respiratory tracing).

Still other methods of taking respiratory tracings, by measuring the excursions of the diaphragm, or of the chest, are mentioned in the text.

After the animal is anesthetized, it is tied to the **dog board,** the one illustrated in figure 93 being a cheap and efficient form. A number of sizes should be on hand for different sized animals (1 × 4 feet for dogs; 8 × 30 inches for rabbits). In operating on the neck the front legs should be turned toward the abdomen; in operating on the chest, toward the head.

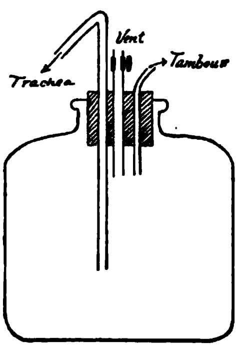

Fig. 92.—Respiration bottle.

Most operations are on the neck. To expose the contents, an incision is made in the median line beginning somewhat below the larynx and extending to near the sternum. The different layers of muscles are carefully separated until the **trachea** is exposed. If it is wished to insert a cannula, two ligatures of stout twine are placed under the trachea an inch or two apart, by means of forceps or an aneurysm needle. Three or four rings of cartilage are then divided by means of a median incision and trimmed off a little on each side, so that the sharp end of the cannula can be inserted. This is then secured by the lower ligature, and the upper one is also tied. If a finger be then passed into the wound and pressed outward from the trachea, the **carotid arteries** can be felt beating. By a little manipulation they can be brought to the surface of the wound so that they can be readily seen. They are isolated from the surrounding tissue by manipulation with the forceps. This can be done without any danger in dogs, but requires some care in rabbits, since the walls are somewhat delicate and are easily torn. The **vagus** is seen as a white cord accompanying the carotid. In the rabbit there are several nerves in this region, of which the vagus is the largest. The nerve should never be included in a ligature with the artery. If it is desired to stimulate it, a ligature should be placed under it, after freeing it from the surrounding tissues. If it is desired to stimulate the central and peripheral ends separately, the nerve should be ligatured in two places and divided between.

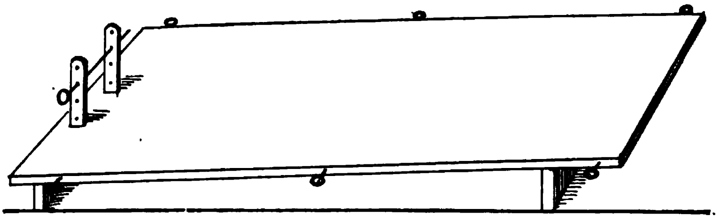
Fig. 93.—Dog board.

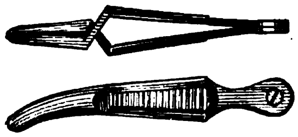
Fig. 94.—Bull-dog clamps.

To insert a cannula into an artery, this must be cleaned as fully as possible. Two ligatures are placed under it an inch apart. A bull-dog clamp (Fig. 94) is applied at the end toward the heart. The peripheral ligature (away from the heart) is then tied firmly. The artery is now partly divided, by sharp scissors, a short distance peripheral to the bull-dog forceps, and the pointed end of a cannula is inserted and secured by the second ligature. In *inserting a cannula into a vein* care must be taken to have the vein well filled with blood. After insertion, the cannula is filled by a long, pointed pipette with normal saline solution and connected with the manometer or injection tube.

The **external jugular vein** is found most easily by making a median incision into the neck and then dissecting backward between the skin and muscles, when it will be encountered.

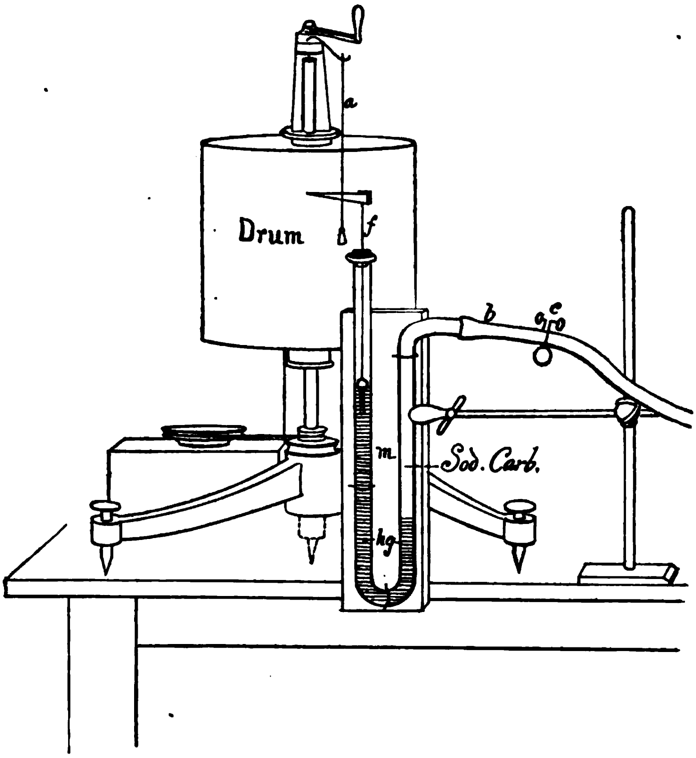

Fig. 95.—Arrangement for taking a blood-pressure tracing (Stewart): *m*, Manometer; *hg*, mercury; *f*, float armed with writing-point; *a*, thread attached to a wire projecting from the drum and supporting a small weight; the thread keeps the writing-point in contact with the smoked paper on the drum; *b* is a strong rubber tube connecting the manometer with the artery; *c*, a pinch-cock on the rubber tube, which is taken off when a tracing is to be obtained.

The **femoral vessels** can be felt just external to the muscle which stands out boldly at a right angle to Poupart's ligament.

The **sciatic nerve** is most easily exposed from the back of the leg. The leg must be flexed and held toward the head. An incision is then made through the skin over the ridge which is formed in this manner. By separating the muscles the sciatic nerve can be felt as a firm cord and can be brought to the surface by hooking the finger under it.

To open the chest, a horseshoe incision is made through the skin, consisting of a cut some distance on either side of the sternum and joined near the clavicles. Stout waxed ligatures are then placed on each rib with an aneurysm needle. A ligature of the same kind is placed around the sternum. **Artificial respiration** is then begun. This can be done by a bellows attached by a T-tube to the tracheal cannula or to one neck of the Woulf's bottle. The open limb of the T is closed during inflation. The ribs are then cut through with bone forceps, to the sternal side of the ligatures. The sternum itself is then divided. Two pairs of artery forceps should be at hand to clamp the bleeding mammary arteries, which can then be tied off.

In taking the **blood pressure** the carotid artery is connected with a mercury manometer (Fig. 95), the connections being filled with a half-saturated solution of magnesium sulphate. Before connecting the apparatus, a pressure of 100 mm. of mercury for dogs, or 70 mm. for rabbits, must be obtained by blowing into the tube, applying a pinchcock, and filling the tube with the solution. Care must be taken that the float works freely. It may be necessary to put a few drops of gasoline with the float to obtain this result. To take tracings, the writing-point is adjusted to a slowly revolving drum, being held against the paper by a silk thread suspended from the frame of the drum, and held taut by a small weight. It is necessary to take direct observations of the height of blood pressure and the rate and character of heart and respiration, as well as tracings.

If there is **clotting** in the cannulæ the apparatus must be disconnected and cleaned. The cannula need not be removed, but can be cleaned *in situ* with the rib of a feather to which a little of the blade has been left attached.

In all animal work the time required to produce results should be noted.

In the experiments on animals, it is well to arrange the students into "sets" of three men for work on frogs, five for mammals. Each man should be placed in charge of some particular part of the experiment: taking records, setting up the apparatus, operating, taking tracings, etc. The reports should be preserved accessible to future classes. When an experiment is arranged in sections, it is intended that each section be done by half the sets. The supplement and dose tables will permit of varying the experiments almost infinitely, at the choice of the instructor.

CHAPTER XXXV.

FROG WORK.

EXPERIMENT I.

CONVULSANTS AND PARALYSANTS.

NOTE *general behavior* of animals. Gross changes in *reflexes* (dipping foot in ⅔ % HCl or 5 % Acetic Acid). Rate of *respiration* and if possible *heart*. Changes in diameter of *pupil*. If *convulsions* appear, note whether they are clonic or tonic. Which muscles are mainly affected. Locate their seat by successive destruction of hemispheres, medulla, and cord. (Ten or fifteen minutes or longer, if possible, must be allowed for recovery from shock, before concluding that the seat of the convulsions has been destroyed.) In the case of *paralysis*, note: Symptoms pointing to lessened activity of hemispheres (quietness, avoidance of obstacles, swimming, croaking); disturbed sensation of equilibrium (incoordination—difficulty in turning); paralysis of respiration; paralysis of extremities. If the animal does not die during the experiment, observe it for several days to notice after-effects. If the reflexes have disappeared, expose the heart and note its state according to Experiment IV, B. Test the excitability of the sciatic nerve and gastrocnemius muscle. If the latter requires a stronger current, the condition is normal; if the former, there is a curare action.

The drugs are injected with a pipette through a small incision made into the skin over the anterior portion of the ventral or dorsal lymph-sac. The quantity of solution should not exceed 0.5 c.c. to 1 c.c., if possible.[1]

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[1] For example: Strychnin ¼ mg.: To have this amount in 1 c.c. (1000 mg.) would require a solution of ¼ : 1000 or 1 : 4000. If a 1 : 5000 solution is furnished, each cubic centimeter = $\frac{1}{5000}$ Gm. Strychnin = 0.2 mg.; to obtain ¼ mg. would require 1¼ c.c. of this solution.

With the frogs marked * the effect of drugs upon the eye can be studied. (See Experiment IV, B.)

Each student use two frogs.

1. *Strychnin,[1] ¼ mg.
   Morphin, 50 mg.
2. Nicotin, 2 mg.
   *Carbolic Acid: place in jar with 1 : 10,000 freshly made solution and compare with control.
3. *Caffein, 5 mg.
   Physostigmin, ½ mg.
4. Picrotoxin, 10 mg. per mouth.
   Cocain, ½ mg.
5. *Cinchonidin, 10 mg.
   Camphor, 0.1 Gm.
6. Atropin, ½ mg.
   KCl, 1 c.c. 10%.
7. Aconite, 1 c.c. 5% solution.
   Ammon. Chlorid. 0.25 Gm.

These doses are calculated for medium-sized frogs (40 Gm.).

Other drugs which may be substituted for the above are:

TABLE XVII.—DOSES FOR (40 Gm.) FROGS.

Aconitin, cryst.	0.5 mg.
Aconitin, amorphous	1 to 200 times the dose of the crystalline.
Anilin	2 drops in mouth.
Apocynum	0.067 Gm.
Cadmium Sulphate, cryst.	0.04 Gm.
Carbolic Acid	1 c.c. 1%.
Cinchonin	10 mg.
Cobalt Nitrate	0.016 Gm.
Convallaria	0.01 Gm.
Conium	2.5 Gm.
Coriamyrtin	0.1 mg.
Digitalis	0.5 Gm.
Ergot	2.0 Gm.
Gelsemium	0.6 Gm.
Helleborus Niger	0.02 Gm.
Hyoscyamus	0.5 Gm.
Ipecac	0.05 Gm.
Lobelia	2.5 Gm.
Phosphorus	¼ mg. suspended in mucilage, per mouth (for fatty degeneration).

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[1] Note the effectiveness of different stimuli in bringing on convulsions. Blowing on the frog or jarring the table will be found amongst the most effective. Sound has no effect. Also note that very weak electric stimuli, just strong enough to cause convulsions if applied to the skin, will not do so if applied to underlying muscle (the muscle of the other leg is best bared previously). Very strong stimuli will, however, start convulsions from here also.

Quinin	10 mg.
Sanguinaria	1.0 Gm.
Sodium Oxalate (neutral)	0.013 Gm.
Sodium Nitrite	0.03 Gm.
Squills	0.04 Gm.
Strophanthus	0.001 Gm.
Veratrin or Protoveratrin	0.25 mg.
Veratrum Viride	0.05 Gm.
Zinc Sulphate, cryst.	0.06 Gm.

EXPERIMENT II.

EFFECT OF DRUGS ON SKELETAL MUSCLE.

Section A.—1 (a). Make a curare experiment. Pith a frog, brain only. Make an incision in the skin on the thigh over the course of the sciatic nerve. Isolate this nerve and pass under it a stout ligature. With this tie off the entire leg with the exception of the nerve. Inject 0.5 to 1 c.c. of 1 : 200 curara solution. Let the frog get under its influence so that it will not draw up the unligated leg on pinching (10 minutes to half an hour). Dip the foot of the sound leg into 5% acetic acid for a short time. Note that the animal does not draw up the sound leg, but the one that is ligated. Wash off the acid. Make two muscle-nerve preparations. Stimulate the nerve of the ligated leg electrically, and increase the distance between the coils to the furthest point at which a good contraction is obtained. Stimulate the nerve of the unligated leg with the same strength of current. The muscle should not contract, even if the current is considerably strengthened. By placing the electrodes directly on the muscle, contractions may be obtained from either leg.

1 (b). Excise both eyes. Place one in N. S.,[1] the other in 1% *Physostigmin* in a dark place, and note size of pupil from time to time.

2 (a). Use gastrocnemii of this experiment to show effects of *caffein.* Arrange coil for single break shocks (p. 776). Use 10 Gm. weight, attached at same distance from pivot as the muscle. Take a normal tracing. Now lay the muscle in 1 : 10,000 Caffein Citr. in N. S. for five minutes. Take another tracing. Repeat with 1 : 1000, then 1 : 100 solution. Let lie in the latter until rigor is obtained. Note the reaction of a cross-section to litmus. Examine the muscle microscopically.

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[1] N. S. = Normal Salt solution (0.75% NaCl for frogs, 0.9% for mammals).

2 (b). On the other muscle determine the maximal load: Suspend a tin bucket in place of the 10 Gm. weight and pour in water until the muscle is just unable to contract. Weigh bucket and water. Repeat after laying in 1 : 10,000, 1 : 1000, and 1 : 100 Caffein solution, each for five minutes.

3. Place one of the other muscles of the frog in 1 : 10,000 *sapotoxin*. Try excitability from time to time.

Section B.—1. Pith frog. Excise both *eyes*. Place one in N. S., the other in 1 % *Cocain*, both in dark place, and observe pupils from time to time.

2. Make two muscle-nerve preparations. Get the effects of *Quinin s.* on skeletal muscle, as 2, Section A. Use 1 : 50,000, 1 : 10,000, 1 : 1000, and 1 : 100 solutions.

3. As 3, Section A.

SUPPLEMENT TO EXPERIMENT II.

1. Curare Experiment: This may be tried with Conium, Camphor, or Lobelia, in the doses of *Experiment I.*

2. Height of Muscular Contraction and Maximal Load: This may be tried with Apomorphin or Physostigmin, 1 : 1000, 500, 200; or Saturated Camphor in normal salt.

EXPERIMENT III.

EFFECT ON MUSCLE AND NERVE (*Continued*).

Section A.—1. Pith a frog. Excise both *eyes*. Place one in N. S., the other in 1 % *Nicotin*, in a dark place. Observe from time to time.

2. Make two muscle-nerve preparations. Lay nerve of one and muscle of other in 0.1 % *Nicotin* (N. S.) in moist chamber (inverted tumbler or bell-jar). Test irritability of muscle and of nerve in both preparations from time to time, noting greatest distance of coils which gives noticeable contraction. (It is better to scarify the sheath of the muscle with a needle before laying it in the Nicotin.)

With another frog try

3. *Pilocarpin* in *eye*, as in 1.

4. 1 % *KCl* on muscle and nerve, as in 2.

5. Take one of the other muscles and lay in 1 % $CaCl_2$ and try excitability from time to time.

Section B.—Inject ¼ mg. *Veratrin Sulphate* or 0.05 c.c. of Fluid Extract Veratrum Viride and note results. As soon as the animal shows typical symptoms, pith and make two muscle-nerve preparations.

1. Excise the *eyes* and place one in N. S., the other in 1 % *Atropin*, in a dark place, and note diameter of pupils from time to time.

2. Get a typical veratrin curve, as in **2** (**a**), Experiment II.

Note the effect of cold, heat (5°, 10°, 20°, 25°, and 35° C.), and fatigue on the form of this curve. (Fatigue is obtained by tetanizing the muscle until it gives only half the original height of contraction.)

SUPPLEMENT TO EXPERIMENT III.

A (**2**): Instead of Nicotin one may use: Camphor, saturated in normal salt; Guanidin, 1 % (N. S.); Lobelia or Conium (1 : 25 N. S.); or Coniin or Lobelin, 0.2 % (N. S.); and the drugs of **2**, Experiment II, or Phosphorus (saturated in N. S.).

B (**2**): The effect of cold, heat, and fatigue may also be studied on the curve of the drugs of **2**, Experiment II.

EXPERIMENT IV.

EFFECT OF DRUGS ON HEART.

Section A.—1. Curarize a frog. (Set up Williams' Apparatus, Fig. 75, p. 488.)

Pin on board to observe circulation in foot (Oc. III, obj. III). Make an exact drawing of a small vessel. Inject into lymph-sac 0.5 c.c. *Tincture* (= 15 %) *Digitalis* and observe the same vessel from time to time and note changes in its diameter.

2. Apply 1 % *Cocain* to one *foot* of another frog and note sensitiveness to mechanical, electric, thermal, and chemic stimuli from time to time. Compare with other foot.

3. Pith the second frog. Pass a thread under bulbus aortæ and introduce cannula into ventricle through cut in aorta and tie with thread; fill cannula with cow's or rabbit's blood diluted with equal volume N. S., or, if this is not obtainable, with an alkaline 2 % solution of Gum Arabic in normal salt. Have one reservoir of the Williams apparatus filled with same blood or solution. Raise reservoir about 6 to 8 inches. Set off apparatus. Observe rate of heart and of drops, and take tracing. Now circulate through heart some blood (or gum solution) containing 1 : 1000 Nicotin. Note effects. When secondary quickening is observed, circulate 1 : 1000 Pilocarpin. If this produces slowing, circulate 1 : 10,000 Atropin. When heart is quickened, circulate 1 : 1000 Physostigmin. Then 1 : 100 Digitalis, all in blood or in the gum solution.

Section B.—Pith seven frogs. Excise the *eyes*, and repeat any of the previous experiments which may have failed, or lay them in 1 : 1000 solution of the following in a dark place: Muscarin, Coniin, Gelseminin, Aconitin, Apomorphin, keeping a control of each in N. S.

Expose the *hearts* and try activity of vagus trunk and of sinus, then apply (in N. S.):

1. Aconite 1 : 25 Drug. Try activity of vagus (trunk and sinus) in the various stages.
2. Veratrin, 1 : 200.
3. Quinin, 1 : 100,000; let act for twenty minutes, then 1 : 5000.
4. Digitalis, 1 : 50 Drug.
5. Barium chlorid, 1 : 100 in water.
6. Apomorphin, 1 : 200.
7. Camphor, saturated solution in N. S.

Renew the applications every five minutes.

When the heart stops, see whether it is in systole, diastole, or median position. Try whether it can be started by lightly pricking with a needle. When this does not succeed, see whether N. S. saturated with camphor, has any effect. (Former = paralysis of automatic mechanism; latter, depression cardiac muscle.) When camphor is not effectual, try 0.1 % Physostigmin. Always note the rate and the strength and regularity of the beats, as well as comparative length of systole and diastole. Try excitability of vagus trunk and sinus from time to time. Note whether stoppage is systolic or diastolic. If the latter, try 0.1 % Atropin.

SUPPLEMENT TO EXPERIMENT IV.

A (1): For Digitalis one may substitute Quinin, Physostigmin, or Nitrites. Another way of performing this experiment is to cut off a toe and note the rate at which the blood drops, before and after injection (curarization would not be necessary).

A (2): In place of Cocain, one may use Eucain, Holocain, Aconitin, Carbolic Acid, Antipyrin—all in a strength of 1%.

A (3): The drugs of B may be used, in about the same strength as given there.

B: The following drugs may be used on the *heart:* Caffein, 1 : 10,000, 1000, 200, 100; KCl, 2%; Cocain, Curare, Nicotin, Coniin, Lobelin, Gelsemin, Spartein, Physostigmin, Pilocarpin, all 1 : 1000; Convallaria, Strophanthus, Apocynum, and the drugs corresponding to the above alkaloids, 1 : 25; Phosphorus, saturated in N. S.

EXPERIMENT V.

The two sections exchange the experiments of IV.

CHAPTER XXXVI.

WORK ON MAMMALS.

EFFECT OF DRUGS UPON INTACT ANIMALS.

The observations must bear on:

(A) Central Nervous System.—1. Stimulations: Exaggeration of reflexes. Excitability, choreiform movements, convulsions (character of convulsions) with or without loss of consciousness.

2. Paralyses: Drowsiness. Incoordination. Paralyses of individual muscles. Depression of reflexes. General muscular paralysis with or without loss of consciousness. Involuntary passage of urine or feces.

(B) Respiration.—Rate and character.

(C) Pupils.—Dimension; reaction to light.

(D) Temperature.—Rectal.

(E) Secretions.—Flow of saliva.

(F) Circulation.—Rate and character of pulse; color of mucous membranes.

(G) Vomiting.—Quickness of action; length of stage of nausea; amount of depression.

(H) Purgation.—Quickness of action; amount and character of stools.

Weight and sex must be stated in all experiments.

The time required to produce an action should be noted.

Whenever death seems imminent, apply the appropriate physiologic antidotes and see whether the animal can be saved.

Drugs given to dogs by stomach should be made up to 25 to 50 c.c.; drugs given to dogs hypodermically should be made up to 1 to 10 c.c.; intravenously, 25 to 75 c.c.; drugs given to rats or guinea-pigs should be made up to 1 to 5 c.c.

EXPERIMENT I.

Section A.—

1. Dog's eye, Atropin, then Physostigmin, each 1%.
2. Tartar Emetic, Dog, Stomach (Emetic), 20 c.c. of ¼%.
3. Rhubarb, Dog, 5 c.c. F. E.,[1] Stomach (Purgative).
4. Hydrocyanic Acid, Guinea, 1 c.c. 1% subcutaneously.
5. Veratrum Viride, Hypodermic, Guinea, ½ c.c. F. E.
6. Hydrochloric Acid, Guinea, Rectal, 50 to 100 c.c. 1%. (When effect is marked, inject 2% Na_2CO_3 intraperitoneally.)

Section B.—

1. Dog's eye, Nicotin, 1%.
2. Ipecac, Dog, Stomach, 1 c.c. F. E. (Emetic).
3. Sulphur, Dog or Guinea, with feed (Purgative).
4. Nicotin, Guinea, small drop on tongue.
5. Morphin, Guinea, 1 c.c. 4% hypodermic.
6. Arsenic, Guinea, hypodermic, 1 c.c. of 1 : 1000 Sod. Arsenate. (Make postmortem, with especial attention to alimentary canal.)

EXPERIMENT II.

Section A.—

1. Dog's eye, Cocain, 1% (Anesthesia and pupil).
2. Copper sulphate, Dog, Stomach, 50 c.c. 1% (Emetic).
3. Elaterin, Cathartic, Dog, Mouth (Purgative), 2 mg.
4. Strychnin, Guinea, hypodermic, 1 c.c. 1 : 400.
5. Strophanthus, F. E., Guinea, hypodermic, 1 c.c. of the twenty times diluted fluid extract.
6. Mercuric chlorid, Rat, 1 c.c. of 1 : 100 hypodermic (make autopsy).

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[1] F. E. = Fluid Extract.

Section B.—

1. Dog's eye, Pilocarpin 1%.
2. $ZnSO_4$, Emetic, Stomach, Dog, 50 c.c. 1% solution.
3. $MgSO_4$, Cathartic, Stomach, Dog, 50 c.c. 5% solution.
4. Aconite, Guinea, hypodermic, 1 c.c. 1 : 150.
5. Cannabis, Dog, Stomach, 10 c.c. of Fluid Extract.
6. Oxalic Acid, Rat or Guinea, 2 c.c. 5% Sod. Oxalate hypodermic. Harden kidneys and examine.

The same Drugs which were used on Frogs' eyes may also be applied to those of Mammals, in 1% solution.

Supplement.—The following drugs may be substituted. These may also be used in the same quantities in the vivisection experiments. The dose is calculated for: Dogs, 5 Kg.; Rabbits, 1 Kg.; Guinea-pigs, 300 Gm.; Rats, 100 Gm. When the dose of the drug is given, the Fluid Extract may be used.

TABLE XVIII.—DOSES FOR MAMMALS.

H = Hypodermic. M = by mouth. V = Intravenous.

DRUG.	DOG.	RABBIT. (When not mentioned = ⅙ dose of dog.)	GUINEA.
Aconite	0.05 Gm. V. 0.1 Gm. H.	. .	0.009 Gm. H.
Aconitin cryst.	0.5 mg. H. 0.3 mg. V.	0.5 mg. H.	. .
The amorphous must be taken (to 200 times) stronger.			
Amyl Alcohol	. .	. .	Inhalation.
Ammonium Chlorid	0.2 Gm. V (in 2% sol.).	. .	1 cc. 30% into peritoneum.
Antipyrin	2 Gm. H.	0.5 Gm. M.	0.15 Gm. H.
Apocynum	. .	. .	3 Gm.
Apomorphin	10 mg. H.	10 mg. H.	. .
Arsenious Acid	25 mg. M.	. .	. .
Atropin	5 mg. H.	. .	0.5 mg.
Barium Chlorid	0.1 Gm. V (in 5% sol.).	. .	. .
Belladonna	0.25 Gm. H.	. .	3 Gm. H.
Benzoic Acid	. .	2.0 Gm. H.	. .
Benzol	. .	10 c.c. H.	. .
Cadmium Sulphate	0.15 Gm. V.	. .	. .
Caffein	0.5 Gm. H.	. .	. .
Calcium Chlorid	5 Gm. V (5% sol.).	. .	. .
Camphor	. .	20 c.c. 20% M.	. .
Cannabis Indica	5 c.c. M.	. .	. .
Carbolic Acid	0.75 Gm. H.	0.5 Gm. H.	0.12 Gm. H.
Cantharidin (Nephritis)	10 mg. H. (dissolved in dil. NaOH).	0.1 mg. H.	0.05 mg. H.

TABLE XVIII.—DOSES FOR MAMMALS.—(*Continued.*)

H = Hypodermic. M = by mouth. V = Intravenous.

DRUG.	DOG.	RABBIT. (When not mentioned = ⅙ dose of dog.)	GUINEA.
Chloral	0.2 Gm. V (in 5% sol.).	. .	. .
Coca	25 c.c. M.	. .	15 Gm. H.
Cocain	0.02 Gm. H. (1%).	0.01 Gm. H.	. .
Cocculus	2.	. .	. .
Colchicum Root	. .	. .	0.075 Gm. H.
Colchicum Seed	. .	. .	0.15 Gm. H.
Conium	0.25 Gm. H.	. .	0.15 Gm. H.
Convallaria	.	. .	0.025 Gm. H.
Curara	50 mg. V (in 0.5% solution).	. .	. .
Digitalis	0.04 to 1 Gm. V (as infusion).	. .	1 Gm. H.
Ergot	5 Gm. H.	. .	. .
Erythrophlein	5 mg. V.	. .	.
Gelsemium	. .	. .	2.0 Gm. H.
Hellebore Niger	. .	. .	0.06 Gm. H.
Heroin	. .	0.5 mg. H.	. .
Hydrastin or Hydrastinin	10 mg. H.	. .	. .
Hydrocyanic Acid	20 mg. H or M.	2 mg. H.	. .
Hyoscyamus	. .	. .	3 Gm. H.
Iodin (Effects on Circulation)	. .	25 c.c. Serum containing ½% iodin. V.	. .
Iodin (Fever)	. .	2 c.c. tincture H.	. .
Ipecac	1 Gm. H.	. .	1.5 Gm. H.
Lobelia	1.25 Gm. H.	. .	3 Gm. H.
Mercuric Chlorid (Nephritis)	1 c.c. of 0.1 % per day, H.		
Nicotin	25 mg. H.	. .	. .
Nitroglycerin	1 mg. H.	. .	. .
Phosphorus	1 c.c. phosphorated oil every second day, M (for fatty degeneration).		
Physostigma	10 mg. H.	. .	. .
Physostigmin	1 Gm. H.	. .	. .
Picric Acid	1 Gm. H.	. .	. .
Picrotoxin	5 mg. H. 0.5 Gm. M.	1.5 mg. H.	1 mg. H.
Pilocarpin	5 mg. H.	. .	. .
Pilocarpus	2.5 Gm. H.	. .	. .
Piperidin	0.1 Gm. H.	. .	. .
Potassium Cyanid	. .	1 mg. H.	. .
Potassium Chlorate	5 Gm. H.	Note Methemoglobin formation.	
Potassium Chlorid	0.5 Gm. (2%) V.	0.1 Gm V.	

TABLE XVIII.—DOSES FOR MAMMALS.—(*Continued.*)

H = Hypodermic. M = by mouth. V = Intravenous.

DRUG.	DOG.	RABBIT. (When not mentioned = ¼ dose of dog.)	GUINEA.
Quinin Hydrochlorate	0.2 Gm. M. 10 mg. H.	(to lower N excretion). (for blood pressure).	
Ricin	. .	0.07 Gm. H.	. .
Santoninate of Soda (Convulsion)	5 Gm. H.	. .	. .
Sanguinaria	. .	. .	3 Gm. H.
Silver Nitrate (for Fever)	. .	2 c.c. 2% H.	. .
Sodium Arsenite	0.5 Gm. V or H (in 5% sol.).	. .	. .
Sodium Chlorid	10% V.	10% V.	. .
Sodium Iodid	. .	25 c.c. 7%.	. .
Sodium Oxalate Neutral	0.5 Gm. H.	0.125 Gm. H.	. .
Sodium Phosphate	. .	2 c.c. 2%.	. .
Spartein Sulphate	0.125 Gm. H.	. .	. .
Squills	0.5 Gm. H.	. .	0.15 Gm. H.
Strophanthus	0.05 Gm. H.	. .	0.005 Gm. H.
Strophanthin	0.5 mg. V.	. .	. .
Strychnin	2 mg. H. 0.75 mg. V.	. .	1.5 Gm. H.
Turpentine (Diuresis)	15 drops, M.	. .	. .
Tobacco	0.5 Gm. H.	. .	. .
Veratrin	10 mg. H.	1.25 mg. H.	. .
Veratrum Viride	0.2 Gm. H.	. .	0.15 Gm. H.
Zinc Sulphate	0.4 Gm. V.	. .	. .

OPERATIVE WORK.

(*To be done on completely anesthetized animals.*)

In the following experiments rabbits or dogs may be used indifferently. In case an animal dies before the experiment is completed, another animal should be supplied, and the new experiment is to be begun where the last one was left off.

Other drugs may be substitued, in the Doses of Table XVIII.

EXPERIMENT III.

EFFECT OF DRUGS UPON RESPIRATION AND BLOOD PRESSURE.

(Mainly Respiration.)

Aconite, Ammonium Chlorid, Carbolic, Na_2SO_4, NaCl.

Operation.—Insert tracheal cannula and connect with bottle and tambour for respiratory tracings. Connect carotid for blood pressure. Insert cannula into central end of jugular or femoral vein, fill with normal salt solution, and connect with burette for injection. Use two drums for taking the tracings.

Experiment.—1. Aconite (therapeutic doses).—Inject hypodermically 0.15 Gm. per Kg. of Aconite (or 1 mg. per Kg. of Aconitin in 2 : 1000 solution). Allow this to act until a slowing of the heart and a fall of blood pressure are obtained.

2. Ammonium Chlorid.—Inject intravenously 0.15 Gm. per Kg., and observe until typical results are obtained.

3. Carbolic Acid.—Inject hypodermically 5 mg. per Kg. in 2 : 1000 solution. Allow this to act until death seems imminent. Meanwhile fill burette with 1% solution of sodium sulphate. When blood pressure has fallen almost to zero, inject rapidly about 25 c.c. per Kg. of the sodium sulphate intravenously.

4. NaCl.—When animal has returned to near normal, run into vein a 10% *solution of sodium chlorid* at the rate of about 1 c.c. per Kg. per minute, until death.

II. Peripheral Action on Blood-vessels.—In this or in any other animal which dies early in the experiment, open the inferior vena cava, connect the central end of the carotid with the injection burette raised fairly high or connected with the pressure apparatus, and inject 50 c.c. of the following, noting the time required for the injection:

Water.	
Chloroform water.	
Digitalis	1 : 100.
$BaCl_2$	1 : 100.
Tartar Emetic	5%.

EXPERIMENT IV.

CARDIOMYOGRAM AND BLOOD PRESSURE.

Curare, Caffein, Nicotin, Atropin, Aconite, NaCl, Suprarenal.

Operation.—Prepare for artificial respiration. Connect carotid for blood-pressure tracings. Put injection cannula into vein. Set up apparatus for cardiomyogram. (Use two drums.) For taking the cardiomyogram, a bent pin is hooked into the apex of the exposed heart. From this a thread passes over a glass rod, which acts as a pulley, to the muscle lever (Fig. 96).

Note after each drug whether stimulation of the vagus is effective on the heart; and of the cervical sympathetic on the pupil, and on the ear vessels. (The sympathetic in the dog runs in the vagus sheath, and it suffices to stimulate the central end of this nerve. In the rabbit it is separate, and forms the middle sized of the three nerves lying near the carotid.)

Experiment.—1.—Inject intravenously 1 c.c. per Kg. of 0.5 % solution of *Curare* every ten minutes till stoppage of respiration. Attempt to revive respiration by inhalation of ammonia or dashing on of cold water. Begin artificial respiration, tap the bladder, and examine the urine for sugar.

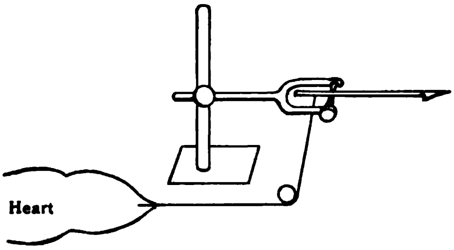

Fig. 96.—Cardiomyograph.

Then expose the heart and connect for myogram. Take normal tracings.

2. Inject subcutaneously 20 mg. per Kg. of *Caffein citrate*. Allow this to act until heart is quickened.

3. Inject subcutaneously 5 mg. per Kg. of *Nicotin* (or 1 c.c. per Kg. of 10% tincture of tobacco). Allow this to act until quickening of the heart is obtained.

4. Inject subcutaneously 1 mg. per Kg. of *Atropin sulphate* (or 0.05 c.c. per Kg. of F. E. Belladonna).

5. In fifteen minutes inject *Aconite*, 1 c.c. per Kg. of the F. E. Allow this to act (up to thirty minutes) until the heart about stops.

6. Meanwhile fill the injection burette with *normal salt solution*; and when this point is reached, inject intravenously about 25 c.c. per Kg. of this.

7. Inject intravenously suprarenal extract corresponding to 0.1 Gm. per Kg. of the dried gland.

8. Kill the animal. Insert a cannula peripherally into the femoral artery of one leg, and inject a few cubic centimeters of *chloroform*. Compare the onset of rigor in this and in the other leg.

In this or any other experiment, the intestine may be removed, and the parasite always seen in the dog placed in N. S. at 40° C. The various *anthelmintics* (see Chap. XXX, F) can be added and the effect on the movements noted.

EXPERIMENT V.

(DOG). EFFECT OF DRUGS (*a*) ON ARTERIAL AND VENOUS PRESSURE. (*b*) AFTER LIGATION OF AORTA AND VENA CAVA.

(*a*) Strychnin, Nitroglycerin, F. E. Ergot, $BaCl_2$.
(*b*) Strophanthus, Strychnin, Chloroform, KCl, Camphor.

(a) Operation.—Connect carotid artery for blood-pressure tracing. Insert cannula into central end of femoral vein and connect with water manometer.

Experiment.—**1.** Inject hypodermically 0.2 mg. per Kg. of *strychnin* sulphate.

2. In ten or fifteen minutes inject hypodermically 1 c.c. per Kg. of 2 : 1000 *nitroglycerin;* or let the animal inhale a few drops of amyl nitrite.

3. In ten minutes inject hypodermically 1.5 c.c. per Kg. of F. E. Ergot (or 15 c.c. per Kg. of 10% Infusion, intravenously).

4. When the effect of these are manifest, inject hypodermically 2 mg. per Kg. of *barium chlorid.*

(b) Operation.—Put cannulas into the other carotid artery and into one jugular vein, and connect them by means of a "Y" piece. Fill the connections with normal salt solution. Connect the remaining piece of the "Y" with a burette and pressure apparatus. Place a screw-clamp on the pressure apparatus (Fig. 48, p. 248) tubing on the side of the artery. Take off the bulldog forceps, thus connecting the artery and vein into a short circulation.

Begin artificial respiration. Open the abdomen and ligate the aorta and vena cava as high as possible (this largely excludes peripheral vessels).

Experiment.—Inject by means of the pressure apparatus and burette into the vein about 10 c.c. of the following solutions, made up with normal salt (the effectiveness of vagus stimulation may be noted):

1. *Strophanthus*, 1 : 2000.

2. When the heart is markedly slowed, inject into the vein *strychnin*, 1 : 50,000.

3. In about ten minutes inject *chloroform* water.

4. If the heart recovers from this, inject about 5 c.c. of 1 % *potassium chlorid* solution every ten minutes. This will cause the pressure to drop suddenly, and the heart will become very irregular, and even stop. It should be attempted to start it again by rhythmic compression of the thorax in the cardiac region. At the same time 10 c.c. of *camphor* water should be injected.

One may also use the following:

Aconite	1 : 500	Digitalis 10 c.c. 10% Infusion	
Aconitin	1 : 50,000	Helleborein	1 : 5000
Atropin	1 : 5000	Nicotin	1 : 200
Apomorphin	1 : 1000	Physostigmin	1 : 5000
Caffein Citrate	1 : 1000	Pilocarpin	1 : 1000
Chloral	1 : 100	Quinin	1 : 3000
Cocain	1 : 2000	Suprarenal (dry)	1 : 30
Digitalin	1 : 10,000	Veratrin	1 : 20,000

EXPERIMENT VI.

EFFECT OF DRUGS UPON DIURESIS, INTESTINAL VESSELS, OUTFLOW FROM VEIN, AND BLOOD PRESSURE.

Normal Salt, Theobromin Salicylate, Chloral, Nitroglycerin, Digitalis, Caffein, Rigor.

I. Operation.—Connect the carotid for blood pressure. Open the abdomen, draw out the bladder, insert a bladder cannula (Fig. 97) (if the animal is a rabbit) by first passing a ligature around the neck of the bladder and then making an incision and tying in the cannula, being careful not to include ureters in the ligature. In the case of dogs insert thin glass tubes directly into the ureters. Connect the burette with the femoral or jugular vein for injection. Count the number of drops of urine per minute.

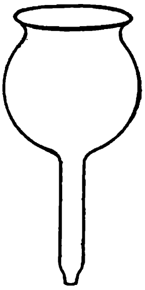

Fig. 97.—Bladder cannula.

Experiment.—1. Inject intravenously 25 c.c. per Kg. of 0.9 % solution of NaCl (or 2 % Na_2SO_4, or water).

2. When the flow of urine diminishes, again inject, hypodermically, 50 mg. per Kg. of *theobromin* salicylate (diuretin).

(If time permits, the ratio of organic constituents and of the different salts in the urine may be determined quantitatively before and after injection.)

Expose the intestine and note its appearance. Cut a small vein, say on the ear, and note the number of drops of blood flowing from it in a unit of time.

3. Inject *Chloral*, 0.5 Gm. per Kg., into stomach. Note especially the effect upon blood pressure and outflow.

4. Inject hypodermically 1 c.c. per Kg. of 1 : 1000 *nitroglycerin*. Observe as above.

5. Inject hypodermically 1 c.c. per Kg. of Tincture of *Digitalis*, and observe the urine and outflow from vein, slowing of the heart, and rise of blood pressure.

6. Then inject 5% Digitalis intravenously until death.

7. Insert a cannula into the peripheral end of femoral vein and inject 2% solution of *Caffein*. Note the onset of rigor in this as compared with the other leg.

II. Drugs on Exposed Intestine.—**1.** Apply to the exposed intestine a drop of 1% solution of Physostigmin.

2. At another place a crystal of NaCl.

3. At another place a crystal of KCl.

4. At another place a drop of 10% Barium Chlorid.

Note the appearance of constrictions, whether they are circumscribed bands or whether they spread and in which direction.

Note whether the constriction is relieved by the application of 1% Atropin or of 1% Apomorphin.

III.—Take other bits of intestine, about two inches long, and place them in 1 : 500 solutions of the following in N. S. at 40° C.:

Nicotin,	then Atropin.
Physostigmin,	" "
Muscarin,	" "
Pilocarpin,	" "
Coniin,	" "

EXPERIMENT VII.

DRUGS ON BLOOD PRESSURE, PERISTALSIS, RESPIRATION (LEVER), PERIPHERAL VESSELS.

Ammonia, Ipecac, Nicotin, Atropin, Physostigmin.

I. Operation.—Connect the carotid for blood pressure. Make an incision in abdomen, and insert a glass rod between the liver and diaphragm. Connect free end with a muscle lever, for respiratory tracings. Use two drums. Note peristalsis and intestinal congestion.

Experiments.—1. Let the animal inhale some *ammonia water*.

2. Inject hypodermically Apormorphin, 1 mg. per Kg.

3. Inject hypodermically 0.1 Gm. per Kg. of *Ipecac*.

4. Inject hypodermically *Nicotin*, 1 mg. per Kg. (or tobacco, 0.2 c.c. per Kg.).

5. *Atropin*, 1 mg. per Kg., or 0.05 c.c. per Kg. F. E. Belladonna.

6. *Physostigmin*, 2 mg. per Kg., or 0.01 Gm. per Kg. of Physostigma.

II. Effect of Drugs upon Peripheral Vessels.—Bleed the animals to death. Rapidly open the thorax and tie a cannula into the peripheral end of the aorta and connect with burette and pressure apparatus. Begin to inject normal salt solution. Insert a cannula into the central end of the femoral vein. Notice how much blood flows out in a unit of time.

Inject, successively, the following drugs, diluted by a mixture of one volume of blood and five volumes of normal salt solution :

Chloral,	1 : 100.
Nitroglycerin,	1 : 1000.
Tincture of Digitalis,	1 : 100.
Hydrastinin,	1 : 1000.
Dried Suprarenal,	1 : 100.

PART IV.

APPENDIX.

I. METHODS OF ANALYZING THE CAUSES OF PHARMACOLOGIC ACTIONS.

An attempt is made in this section to bring together the more important methods employed in pharmacologic research.

For the action of Drugs on the Mammalian Heart see page 246; Intestine, see page 205; Pupil, see page 254; Glands, see pages 252 and 271; Urine, see page 507; Temperature, see page 347.

As a rule, it is first determined whether a given action is the result of a paralysis or of a stimulation. If the former, it is abolished by stimulation—if the latter, by paralysis—beyond the seat of the action. By successive stimulation or paralysis of the different structures which may be involved, the exact seat of the action is then located. But in doing this, it must be borne in mind that a very strong stimulation may overcome a weak paralysis.

Stimulation may be done electrically or by drugs; paralysis, by drugs, section, or excision (or temporarily by the application of cocain).

I. ACTION OF DRUGS ON THE FROG'S HEART.

The action is *nervous* when it cannot be obtained typically after atropin; *muscular* if atropin does not interfere.

I. A Drug produces **Standstill.** The heart may be in

(A) **Medium Position = Paralysis of Muscle.** It cannot be started, or will at most give a few beats, when 0.1 % Atropin, saturated Camphor, and electric stimulation are applied. If it contracts at all, the paralysis involves mainly the rhythmic property.

Here belongs the final action of almost all poisons except those under (C); especially Apomorphin, Copper, Aconite, Chloral, Quinin, Cocain, Carbolic group.

(B) Systolic Position = Overstimulation of Muscle: Until it goes into rigor, the heart can contract against a large resistance if forcibly distended. The condition is preceded by arhythmia and peristaltic contraction.

Here belongs the Digitalis group, also veratrin, barium, alkalies, etc.

(C) Diastolic Position = Stimulation of Vagus Mechanism. It can be removed by 0.1 % Atropin:

The seat of the stimulation may be:

1. Central: The heart beats again if the vagus trunk is divided.

(Picrotoxin.)

2. Preganglionic: (1) is ineffectual, but the heart beats again if 0.1 % Nicotin is applied.

(Pilocarpin.)

3. Postganglionic: (1) and (2) are ineffectual, but the heart beats again if 0.1 % Atropin is applied.

(Muscarin, Physostigmin.)

II. A Drug Produces Quickening or Strengthening.—The effect is probably a *stimulation of the cardiac muscle*. If so, it can be reproduced after atropin. A stimulation of the accelerator endings cannot at present be excluded.

Here belong the early stages of most poisons, particularly Digitalis series, Physostigmin, Camphor, etc.

III. A drug produces little, if any, change in the normal heart, but prevents the effects of stimulation of the inhibitory mechanism:

1. *At the sinus = Paralysis of vagus endings.*
   (Atropin.)
2. Not at (1), but at *the vagus trunk = Paralysis of vagus ganglia.*
   (Nicotin, Coniin, Cocain, Curare.)

II. FROG'S REFLEXES, ETC.

I. The reaction time is shortened: This may be due to—

(A) Increased reflex excitability of the cord—occurs after section of medulla.

(Strychnin, Caffein, etc.)

(B) Lessening of higher inhibition—does not occur after section of the medulla.

II. The reaction time is slowed or all reaction is abolished—

(A) **No matter where the stimulus is applied:**

1. Depression of the Reflex Activity of the Cord.—Stimulation of sciatic causes contraction.

(Carbolic Acid, Camphor in frog, and most depressant poisons.)

2. Curare Action.—Stimulation of the nerve is less effective than stimulation of the muscle.

(Curare-Nicotin series.)

3. Paralysis of Muscle.—Direct stimulation of the muscle is ineffective. The muscle may be:

(*a*) *Paralyzed:* it is soft and usually has an alkaline reaction.

(Copper—very strong doses of most drugs.)

(*b*) *In Rigor:* it is hard and has an acid reaction.

(Caffein.)

(B) The reflexes are diminished **only from those parts which have been touched** by the drug. There is a paralysis of the afferent nerves. This may be in:

1. The nerve-fibers: Obtained best on subcutaneous injection and lasts long.

(Sapotoxin.)

2. The nerve endings: Equally well on painting on the surface; short.

(Cocain.)

III. The frog keeps the part to which the poison has been applied in **constant movement:** local sensory irritation, pain.

(Acids.)

III. FROG'S MUSCLE-NERVE CHAIN.

The intact animal shows:

I. Motor Paralysis. This may be:

(A) **Central:** Stimulation of the nerve is still effective. The seat may be in:

1. The Brain: The reflexes are still active. The phenomena produced by paralysis at different levels are given under Morphin, page 198.

(Early stages of all narcotics.)

2. The Cord: No reflexes.

(Camphor, Quinin, Carbolic, Cocain, etc.)

(B) **Peripheral**: Stimulation of the nerve-trunk has no effects. The paralysis may be in the endings or muscle, see page 806, **II**, **A.**

II. Motor Stimulation. This may be:

(A) **Central**: Abolished by successive destruction of the central nervous system. The exact location may in this way be noted. It should be recorded whether the convulsions are idiopathic or reflex.

(Medulla = Picrotoxin; Cord = Strychnin, Caffein; Brain = Atropin, Cocain.)

(B) **Peripheral**: Not abolished by section of the nerve; usually consists in twitching or increased force or lengthened time of contraction It may be in:

1. The Endings: Abolished by Curare.

(Nicotin, Aconitin, etc.)

2. The Muscle-fibers: Not so abolished.

(Physostigmin, Veratrin, Caffein.)

IV. ON ARTERIAL BLOOD PRESSURE.

I. The Pressure Rises. This may be due to:

(A) **Increased Efficiency of the Heart**: The pressure rises in both arteries and veins. No diminution in size of organs.

(B) **Vasoconstriction.** The seat of the stimulation may be:

1. **Central**: Different vascular areas are variously affected. The venous pressure rises in the leg if the drug is injected after section of the sciatic. To distinguish between the different parts of the nervous axis, these may be cut successively, or blocked.

(Strychnin, Caffein, etc.)

Stimulation may be *reflex* or from *convulsions* or *asphyxia.* These must be excluded.

2. **Peripheral**: Constriction occurs in all areas. Effect the same after section of sciatic nerve. The stimulation may be in:

(*a*) *The nerve endings:* No constriction can be obtained in excised organs after a short time.

(Suprarenal.)

(*b*) *The muscle:* The constriction persists much longer.

(Ergot.)

II. The Pressure Falls. This may be due to :

(A) **Diminished Efficiency of the Heart:** The venous pressure falls in both arteries and veins. No increase in size of organs. The pressure remains low, even if aorta is clamped.

(B) **Vasomotor Paralysis:** The seat of this may be:

1. **Central:** The stimulation of the peripheral end of splanchnic or sciatic causes rise in pressure in the part supplied. The drug has little effect if used after chloral. Asphyxia does not produce any rise.

(Chloral, Chloroform.)

2. **Peripheral:**

(*a*) *Nerve endings* are paralyzed : The dilatation is greatest in areas rich in vasomotor nerves.

(Nitrites.)

(*b*) *Muscle-fibers* are paralyzed : The dilatation is general.

(Nitrites.)

(*c*) *Capillaries* are paralyzed: Edema is easily produced by the intravenous injection of large quantities of normal salt solution. Stimulation of peripheral end of vasoconstrictor nerves still effective.

(Metals.)

V. INCREASED RESPIRATION.

I. Stimulation of the Respiratory Center may be due to :

(A) **Insufficient Oxidation of the Blood:**

1. **Through mechanical hindrance:** The volume of air does not correspond to the violence of the effort. The obstruction may be by:

(*a*) *Mucus:* Râles.

(Pilocarpin.)

(*b*) *Constriction of the bronchial muscles.* The latter may be *direct* or *reflex.* Reflex stimulation would be abolished by section of the vagi.

2. **Through changes in the circulation:** inefficient work of the heart or vasodilatation.

(Cardiac depressant.)

3. **Through chemic changes:**

(*a*) *In the blood* (as Methemoglobin formation, see p. 372).

(*b*) *Increased tissue waste:* Increased CO_2 and N excretion.

(Hyperpyrexia.)

(B) Reflexly from Pain or Convulsions.

(Strychnin.)

(C) Direct Stimulation by the drug: shown by exclusion of the above. The respiratory reflexes are unusually active.

(Strychnin, Caffein, Ammonia.)

II. Diminished Respiration may be from:

(A) Paralysis of the Muscles or Endings: Stimulation of the muscle or of the phrenics not effectual.

(Curare.)

(B) Apnea: disappears in a short time.

(C) Paralysis of the Center:

1. Through Anemia: Disappears if the aorta is clamped.

(Nitrites.)

2. Direct: Through exclusion. The paralysis may be *primary* (Ether), or it may be *secondary* to asphyxia; *i. e.*, preceded by dyspnea (CO).

3. Reflexly: Irritant vapors.

(Ammonia.)

II.

TABLE XIX.—THE CRUDE ORGANIC DRUGS BY ORDERS.

(Adapted from Maisch's "Organic Materia Medica.")

I. Of Animal Origin.

ORDER.	ORIGIN.	DRUG.	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Mammalia:				
Rodentia	Castor Fiber.	Castoreum.	Preputial follicles.	Volatile oil. Reflex medullary stimulants.
Carnivora . . .	Viverra Zibetha.	Civet.	Special glands.	Volatile oil. Reflex medullary stimulants.
Ruminantia . .	Moschus moschiferus.	Moschus.	Preputial follicles.	Volatile oil. Reflex medullary stimulants.
	Bos Taurus.	Fel Bovis.	Bile.	Cholagogue cathartic.

THE CRUDE ORGANIC DRUGS BY ORDERS (OF ANIMAL ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Mammalia:				
Ruminantia . .		Lac Vaccinum.	Milk.	Nutrient.
		Butyrum.	Butter.	Nutrient. Emollient.
		Gelatina.	Gelatin.	Nutrient. Demulcent.
	Ovis Aries.	Sevum.	Suet.	Emollient.
		Adeps Lanæ Hydrosus.	Wool-fat.	"
Pachydermata .	Sus scrofa.	Pepsinum.	. . .	Ferment.
		Pancreatinum.	. . .	"
		Adeps.	Fat.	Emollient.
Cetacea	Physeter macrocephalus.	Cetaceum.	Fat.	"
		Ambra grisea.	. . .	Perfume.
Aves:				
Gallinæ	Gallus Bankiva.	Ovum.	Egg.	Nutrient.
		Albumen Ovi.	White of egg.	Nutr'nt } Pharmacy.
		Vitellus Ovi.	Yolk of egg.	Nutr'nt
		Ingluvin.	Ferment from crop.	Ferment.
Pisces:				
Teleostia	Gadus Morrhua.	Oleum Morrhuæ.	Oil expressed from liver.	Nutrient.
Sturiones . . .	Acipenser Huso.	Ichthyocolla.	Gelatin from swimming bladder.	Protective.
Insecta:				
Hymenoptera .	Apis mellifica.	Cera flava. Cera alba.	} Wax.	Emollient.
		Mel despumatum.	Honey.	Saccharine flavor.
Coleoptera . . .	Cantharis vesicatoria.	Cantharis.	Dried animal.	Cantharidin.
	Cantharis vittata.	(Potato fly.)		
	Epicauta Gorhami.		Dried animal.	"
	Mylabris cichorii.	-	Dried animal.	"
	Blatta orientalis.	(Cockroach.)	Dried animal.	"
Hemiptera . . .	Coccus Cacti.	Coccus.	Dried animal.	Pigments.

II. Of Vegetable Origin.

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Ranunculaceæ . .	Anemone pratensis.		Herb.	Cantharidin.
	Anemone Hepatica.		Leaves.	"
	Ranunculus bulbosus.		Herb.	"
	Coptis trifolia.	(Golden-thread.)	Herb.	Hydrastin.

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[1] When the name of the drug is not given, it is identical with the generic name of the plant.

THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Ranunculaceæ . .	Hydrastis Canadensis.	Hydrastis (Golden seal).	Rhizome and roots.	Hydrastin.
	Helleborus niger.		Rhizome and roots.	Digitalis.
	Nigella damascena.		Seed.	Nicotin.
	Delphinium Staphisagria.		"	Aconite.
	Delphinium Consolida.		"	"
	Aconitum Napellus.	Aconitum.	Root (and leaves).	"
	Aconitum ferox.		Root.	"
	Actæa alba.		Rhizome and roots.	Astringent bitter.
	Cimicifuga racemosa.	Cimicifuga.	Rhizome and roots.	Astringent bitter.
	Xantorrhiza apii folia.		Rhizome and roots.	Astringent bitter.
Magnoliaceæ . .	Drimys Winteri.		Bark.	Aromatic oils.
	Illicium verum.	(Star anise.)	Fruit and volatile oil.	" "
	Magnolia glauca.		Bark.	" "
	Liriodendron Tulipifera.	(Tulip tree.)	Bark.	" "
Menispermaceæ .	Jateorrhiza palmata.	Colombo.	Root.	Bitter.
	Menispermum Canadense.	(Moonseed.)	Rhizome.	"
	Chondodendron tomentosum.	Pareira.	Root.	"
	Anamirta paniculata.	Cocculus Indicus.	Fruit.	Picrotoxin.
Berberidaceæ . .	Berberis vulgaris.		Root and root bark.	Bitter.
	Berberis aquifolium.		Rhizome and roots.	"
	Caulophyllum thalictroides.	(Blue Cohosh.)	Rhizome and roots.	Saponin.
	Podophyllum peltatum.	(Mandrake.)	Rhizome.	Anhydrid cathartics.
Nymphæaceæ . .	Nuphar advena.	(Yellow pond lily.)	Rhizome.	Gummy demulcent.
	Nymphæa odorata.	(Water lily.)	Rhizome.	Gummy demulcent.
Papaveraceæ . . .	Papaver somniferum.	(Poppy) Opium.	Fruit.	Morphin.
			Milk juice (opium).	
			Seed.	
			Fixed oil of seed.	Fatty emollient.
	Sanguinaria Canadensis.	(Blood-root.)	Rhizome.	Morphin.
	Chelidonium majus.	(Celandine.)	Herb.	"
	Dicentra Canadensis.		Tuber.	Bitter.
Cruciferæ	Cochlearia Armoracia.	(Horse-radish.)	Root.	Mustard oil.
	Brassica nigra.	Sinapis nigra (Mustard).	Seed and volatile oil.	" "
			Fixed oil from seed.	Fatty emollient.

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THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Cruciferæ	Brassica alba.	Sinapis alba.	Seed.	Mustard oil.
			Fixed oil from seed.	Fatty emollient.
	Brassica Rapa.	(Rape.)	Fixed oil from seed.	Fatty emollient.
	Capsella Bursa-pastoris.		Herb.	Mustard oil.
Cistineæ	Helianthemum Canadense.		Herb.	Bitter astringent.
Violarieæ	Viola tricolor.	(Pansy.)	Herb.	Bitter.
Canellaceæ	Canella alba.		Bark.	Bitter aromatic.
	Cinnamodendron corticosum.		Bark.	" "
Polygaleæ	Polygala Senega.	Senega.	Root.	Saponin.
	Krameria triandra.	Krameria.	Root.	Tannin.
Caryophylleæ . .	Saponaria officinalis.	(Soap-wort.)	Root.	Saponin.
Hypericineæ . . .	Hypericum perforatum.		Herb.	Tannin.
Guttiferæ	Garcinia Hanburii.	Cambogia (Gamboge).	Gum resin.	Anhydrid cathartics.
Ternstrœmiaceæ	Camellia Thea.	(Tea.)	Leaves.	Caffein.
Dipterocarpeæ . .	Dryobalanops Camphora.	(Borneo camphor.)	Stearoptene.	Camphor.
	Dipterocarpus turbinatus.	(Gurjun Balsam.)	Oleoresin.	Turpentine.
Malvaceæ	Althæa officinalis.	(Marshmallow.)	Root.	Gummy demulcent.
	Althæa rosea.		Flowers.	Gummy demulcent.
	Malva sylvestris.		Flowers.	Gummy demulcent.
	Gossypium herbaceum.	(Cotton) Gossypii Radicis Cortex.	Root bark.	Ergot.
		Oleum Gossypii.	Fixed oil from seed.	Fatty demulcent.
Sterculiaceæ . .	Cola acuminata.		Seed.	Caffein.
	Theobroma Cacao.		Seed.	"
			Fatty oil.	Emollient.
Tiliaceæ	Tilia Americana.	(Linden.)	Flowers.	Gummy demulcent.
Lineæ	Linum usitatissimum.	(Flaxseed.)	Seed and fixed oil.	Gummy demulcent and fatty emollient.
	Erythroxylon Coca.	Erythroxylon.	Leaves.	Cocain.
Zygophylleæ . . .	Guaiacum officinale.	Guaiacum and Guaiaci Resina.	Wood and resin.	Resinous diuretics.
Geraniaceæ . . .	Geranium maculatum.	Geranium.	Rhizome.	Tannin.
Rutaceæ	Cusparia febrifuga.	Angostura.	Bark.	Aromatic bitter.
	Ruta graveolens.	Ruta.	Herb and volatile oil.	Emmenagogue volatile oil.
	Barosma betulina.	Buchu.	Leaves.	Astringent bitter.
	Xanthoxylum Clava-Herculis.	Xanthoxylum (Prickly Ash).	Bark and fruit.	Aromatic bitter.
	Pilocarpus Selloanus.	Pilocarpus.	Leaves.	Pilocarpin.
	Citrus Limonum.	(Lemon.)	Fruit, rind, and volatile oil.	Aromatic.

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THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Rutaceæ	Citrus Bergamia.	(Bergamot.)	Volatile oil.	Aromatic.
	Citrus vulgaris.	(Bitter orange.)	Flowers, fruit, rind, and volatile oil.	"
	Citrus Aurantium.	(Sweet orange.)	Rind and volatile oil.	"
Simarubeæ	Simaruba officinalis.	Simaruba.	Bark.	Bitter.
	Picræna excelsa.	Quassia.	Wood.	"
	Quassia amara.	"	Wood.	"
Burseraceæ . . .	Boswellia Carterii.	Olibanum (Frankincense).	Gum resin.	Perfume resins.
	Commiphora Myrrha.	Myrrha.	Gum resin.	Carminative resin.
	Canarium commune.	Elemi.	Oleoresin.	Resin for plasters.
	Amyris elemifera.	"	Oleoresin.	Resin for plasters.
Meliaceæ	Melia Azedarach.	Azedarach.	Root bark.	Anthelmintic.
Ilicineæ	Ilex opaca.	(Holly.)	Leaves.	Astringent bitter.
	Ilex paraguayensis.	(Maté.)	Leaves.	Caffein.
	Ilex verticillata.	(Black alder.)	Bark.	Astringent bitter.
Celastrineæ . . .	Euonymus atropurpureus.	(Wahoo.)	Bark.	Digitalis (cathartic).
Rhamnaceæ . . .	Rhamnus Frangula.	Frangula.	Bark.	Cathartin.
	Rhamnus Purshiana.	(Cascara Sagrada.)	Bark.	"
Ampelideæ . . .	Vitis Vinifera.	Uva passa (Raisin).	Fruit.	Saccharine demulcent.
Sapindaceæ . . .	Paullinia sorbilis.	Guarana.	Dry paste.	Caffein.
Anacardiaceæ . .	Anacardium occidentale.		Fruit.	Cantharides.
	Rhus Toxicodendron.	(Poison ivy.)	Leaves.	"
	Rhus glabra.	Sumach.	Fruit.	Acid astringent.
	Pistacia Lentiscus.	Mastiche.	Resin.	Plaster resin.
Coriarieæ	Coriaria myrtifolia.		Leaves.	Picrotoxin.
Leguminoseæ . .	Baptisia tinctoria.		Root.	Dyes.
	Cytisus Scoparius.	Scoparius.	Twigs.	Aromatic diuretics.
	Trigonella Fœnumgræcum.	(Fenugreek.)	Seeds.	Carminative essential oil.
	Melilotus officinalis.	(Sweet clover.)	Herb.	Aromatic oil.
	Astragalus gummifer.	Tragacantha.	Tragacanth.	Gummy demulcent.
	Glycyrrhiza glabra.	(Licorice.)	Root.	Sweet demulcent.
	Arachis hypogæa.	(Peanut.)	Fixed oil.	Oily emollient.
	Abrus precatorius.	(Jequirity.)	Seed.	Irritant toxalbumin.
	Physostigma venenosum.	Physostigma.	Seed.	Physostigmin.
	Pterocarpus Marsupium.	Kino.	Gum.	Tannin.
	Pterocarpus Santalinus.	Santalum rubrum.	Wood.	Dye.
	Piscidia Erythrina.	(Jamaica dogwood.)	Bark.	Alkaloidal hypnotic.

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The Crude Organic Drugs by Orders (of Vegetable Origin).—(*Continued.*)

Order.	Origin.	Drug.[1]	Part Used.	Group to which the Drug Mainly Belongs.
Leguminosæ	Dipteryx odorata.	(Tonka bean.)	Seed.	Aromatic oil.
	Toluifera Pereiræ.	Balsamum Peruvianum.	Balsam.	Aromatic resin.
	Toluifera Balsamum.	Balsamum Tolutanum.	Balsam.	" "
	Hæmatoxylon campechianum.	(Logwood.)	Wood.	Tannin. Dye.
	Cassia Fistula.		Fruit.	Cathartin.
	Cassia acutifolia.	Senna.	Leaves.	"
	Cassia angustifolia.	"	Leaves.	"
	Cassia Marilandica.	"	Leaves.	"
	Tamarindus Indica.		Fruit pulp.	"
	Copaiba Langsdorffii.	Copaiba.	Oleoresin.	Aromatic resins
	Erythrophlœum Guineense.	(Sassy bark.)	Bark.	Digitalis.
	Acacia Catechu.	Catechu.	Gum.	Tannin.
	Acacia Senegal.	Acacia.	Gum.	Gummy demulcent.
Rosaceæ	Amygdalus communis.	(Almond seed.)	Seed, fixed and volatile oils.	Oily emollient; hydrocyanic.
	Prunus Persica.	(Peach leaves.)	Leaves.	Hydrocyanic.
	Prunus domestica.	(Prunes.)	Fruit.	Saccharine demulcent and cathartic.
	Prunus serotina.	Prunus Virginiana.	Bark.	Hydrocyanic.
	Prunus Laurocerasus.	(Cherry laurel.)	Leaves.	"
	Spiræa tomentosa.		Herb.	Aromatic oil.
	Quillaja Saponaria.	Quillaja.	Bark.	Sapotoxin.
	Rubus Idæus.	(Raspberry.)	Fruit.	Saccharine demulcent.
	Rubus villosus.	(Blackberry.)	Root bark and fruit.	Tannin.
	Geum rivale.		Rhizome and roots.	"
	Geum urbanum.	(Avens.)	Rhizome and roots.	"
	Fragaria vesca.	(Strawberry.)	Rhizome.	"
	Potentilla Canadensis.	(Cinquefoil.)	Herb.	"
	Potentilla Tormentilla.		Rhizome.	"
	Hagenia abyssinica.	Kusso.	Inflorescence.	Anthelmintic.
	Agrimonia Eupatoria.		Herb.	Astringent bitter.
	Rosa canina.		Fruit.	Perfume.
	Rosa gallica.		Petals.	"
	Rosa centifolia.		Petals.	"
	Rosa damascena.		Volatile oil.	"
Saxifragaceæ	Heuchera Americana.	(Alum root.)	Root.	Tannin.
	Hydrangea arborescens.		Root.	Diuretic.
Droseraceæ	Drosera rotundifolia.		Herb.	Ferment.
Hamamelideæ	Hamamelis Virginiana.	(Witch-hazel.)	Bark and leaves.	Tannin, volatile oil.

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THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Hamamelideæ . .	Liquidambar orientalis.	Styrax.	Balsam.	Aromatic resin.
	Liquidambar Styraciflua.	Sweet gum.	Balsam.	" "
Myrtaceæ	Melaleuca Cajuputi.	Oleum Cajuputi.	Volatile oil.	Turpentine,
	Eucalyptus globulus.	Eucalyptus.	Leaves and volatile oil.	"
	Eucalyptus rostrata.	Kino.	Exudation.	Tannin.
	Myrcia acris.	(Bay leaves.)	Leaves.	Aromatic.
	Eugenia aromatica.	Caryophyllus (Cloves).	Flower, bud, fruit and volatile oil.	"
	Pimenta officinalis.	(Allspice.)	Fruit.	"
Lythrarieæ . . .	Punica Granatum.	(Pomegranate.)	Bark.	Anthelmintic.
Onagrarieæ . . .	Epilobium angustifolium.		Herb.	Tannin.
	Œnothera biennis.		Herb.	"
Turneraceæ . . .	Turnera diffusa.	Damiana.	Leaves.	Volatile oil (aphrodisiac).
Cucurbitaceæ . .	Cucumis Citrullus.	(Watermelon.)	Seed.	Anthelmintic, demulcent.
	Cucumis Melo.	(Melon.)	Seed.	Anthelmintic, demulcent.
	Cucumis sativus.	(Cucumber.)	Seed.	Anthelmintic, demulcent.
	Citrullus Colocynthis.	Colocynthis.	Fruit.	Anhydrid cathartics.
	Ecballium Elaterium.	Elaterium.	Arsinous deposit.	Anhydrid cathartics.
	Cucurbita Pepo.	(Pumpkin.)	Seed.	Anthelmintic, demulcent.
	Bryonia alba.	Bryonia.	Root.	Anhydrid cathartics.
Cacteæ.	Cactus grandiflorus.		Flowering branches.	"Cardiac stimulant."
Umbelliferæ . . .	Conium maculatum.	(Water hemlock.)	Leaves and fruit.	Coniin.
	Carum Ajowan.		Fruit.	Camphor.
	Apium graveolens.	(Celery.)	Fruit.	Aromatic carminative.
	Carum Carvi.	(Caraway.)	Fruit.	Aromatic carminative.
	Carum Petroselinum.	(Parsley.)	Root and fruit.	Aromatic carminative.
	Pimpinella Anisum.	(Anise.)	Fruit.	Aromatic carminative.
	Fœniculum vulgare.	(Fennel.)	Fruit.	Aromatic carminative.
	Archangelica officinalis.		Root.	Aromatic carminative.
	Archangelica atropurpurea.		Root.	Aromatic carminative.
	Peucedanum graveolens.	Anethum (Dill).	Fruit and volatile oil.	Aromatic carminative.
	Peucedanum Ostruthium.	Imperatoria.	Root.	Aromatic carminative.
	Opopanax Chironium.		Gum resin.	Aromatic carminative.
	Coriandrum sativum.	Coriandrum.	Fruit.	Aromatic carminative.
	Cuminum Cyminum.		Fruit.	Aromatic carminative.

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THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Umbelliferæ . . .	Daucus Carota.	(Carrot seed.)	Fruit.	Aromatic carminative.
	Ferula Narthex.	Asafœtida.	Gum resin.	Stimulant oil (antihysteric).
	Ferula galbaniflua.	Galbanum.	Gum resin.	Stimulant oil (antihysteric).
	Ferula Sumbul.	Sumbul.	Root.	Stimulant oil (antihysteric).
	Ferula tingitana.		Gum resin.	Stimulant oil (antihysteric).
	Dorema Ammoniacum.	Ammoniacum.	Gum resin.	Stimulant oil (antihysteric).
Araliaceæ	Aralia spinosa.		Bark.	Aromatic carminative.
	Aralia racemosa.		Rhizome and roots.	Aromatic carminative.
	Aralia nudicaulis.		Rhizome.	Aromatic carminative.
	Aralia quinquefolia.	Panax (Ginseng).	Root.	Aromatic carminative.
Cornaceæ	Cornus florida.	Cornus (Dogwood).	Bark.	Astringent bitter.
Caprifoliaceæ . .	Sambucus Canadensis, etc.	(Elder.)	Flowers.	Aromatic demulcent.
	Viburnum prunifolium.		Bark.	Valerian.
	Viburnum opulus.		Bark.	"
	Triosteum perfoliatum.	Triosteum.	Rhizome and roots.	Emetin (?).
Rubiaceæ	Uncaria Gambir.	Catechu pallidum (Terra japonica).	Extract.	Tannin.
	Cinchona Calisaya.	Cinchona.	Bark.	Quinin.
	Remijia pedunculata.		Bark.	"
	Remijia Purdieana.		Bark.	"
	Ladenbergia, Exostemma.		Bark.	"
	Coffea Arabica.		Seed.	Caffein.
	Cephælis Ipecacuanha.	Ipecacuanha.	Root.	Emetin.
	Mitchella repens.	(Mitrewort.)	Herb.	Saponin.
	Rubia tinctorum.	(Madder.)	Root.	Dye.
	Galium Aparine.	(Cleavers.)	Herb.	Astringent.
Valerianeæ . . .	Valeriana officinalis.	Valeriana.	Rhizome and roots.	Valerian.
Compositæ	Eupatorium perfoliatum.	Eupatorium (Boneset).	Herb.	Aromatic bitter.
	Grindelia robusta.		Herb.	Resin. Antiasthmatic. Specific in Rhus.
	Grindelia squarrosa.		Herb.	
	Solidago odora.	(Golden rod.)	Herb.	Aromatic carminative.
	Erigeron Philadelphicus.		Herb.	Aromatic.
	Gnaphalium polycephalum.		Herb.	Aromatic bitter.
	Inula Helenium.	Inula (Elecampane).	Root.	" "
	Helenium autumnale.		Herb.	" "
	Anacyclus Pyrethrum.	Pyrethrum.	Root.	Saponin.

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THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Compositæ . . .	Achillea Millefolium.	(Yarrow.)	Herb.	Aromatic bitter.
	Anthemis nobilis.	(Chamomile.)	Flowers.	" "
	Anthemis arvensis.		Flowers.	" "
	Anthemis Cotula.		Herb.	" "
	Chrysanthemum Parthenium.		Herb.	" "
	Chrysanthemum cinerariæfolium.		Flowers.	" "
	Matricaria Chamomilla.		Flowers.	" "
	Tanacetum vulgare.	(Tansy.)	Herb.	Aromatic bitter, anthelmintic.
	Artemisia Absinthium.		Herb.	Aromatic bitter, anthelmintic.
	Artemisia vulgaris.		Herb.	Aromatic bitter, anthelmintic.
	Artemisia pauciflora.		Flower buds.	Aromatic bitter, anthelmintic.
	Tussilago Farfara.		Leaves.	Bitter, gummy demulcent.
	Arnica montana.	Arnica.	Rhizome, roots, and flowers.	Aromatic, vulnerary.
	Calendula officinalis.		Herb and florets.	Aromatic bitter.
	Arctium Lappa.	Lappa (Burdock).	Root.	Bitter demulcent.
	Cnicus benedictus.	(Thistle.)	Herb.	Bitter aromatics.
	Carthamus tinctorius.		Florets.	Dye.
	Cichorium Intybus.	(Chicory.)	Root.	Aromatic bitter.
	Taraxacum Dens-leonis.	Taraxacum.	Root.	Demulcent bitter.
	Lactuca virosa.	(Lettuce juice.)	Exudation.	Hypnotic (Cannabis).
Campanulaceæ. .	Lobelis inflata.	Lobelia.	Herb.	Nicotin.
Ericaceæ	Arctostaphylos Uva-ursi.	Uva Ursi.	Leaves.	Arbutin, tannin.
	Arctostaphylos glauca.		Leaves.	Arbutin, tannin.
	Gaultheria procumbens.	Gaultheria.	Leaves.	Flavor; salicylic.
	Epigæa repens.	(Trailing arbutus.)	Leaves.	Arbutin, tannin.
	Kalmia latifolia.	(Mountain laurel.)	Leaves.	Arbutin, tannin, toxic principle.
	Ledum latifolium.		Leaves.	Aromatic astringent.
	Chimaphila umbellata.	Pipsissewa.	Leaves.	Aromatic astringent.
Ebenaceæ	Diaspyros Virginiana.	(Persimmon.)	Fruit.	Tannin; veget. acid.
Styraceæ.	Styrax Benzoin.	Benzoinum.	Resin.	Aromatic resin.
Oleaceæ	Fraxinus Americana.		Bark.	Astringent bitter.
	Fraxinus Ornus.	Manna.	Exudation.	Saccharine demulcent.
	Olea Europæa.	Oleum Olivum.	Fixed oils.	Fatty emollient.

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The Crude Organic Drugs by Orders (of Vegetable Origin).—(*Continued.*)

Order.	Origin.	Drug.[1]	Part Used.	Group to which the Drug Mainly Belongs.
Apocynaceæ . . .	Aspidosperma Quebracho-blanco.		Bark.	Apomorphin.
	Nerium Oleander.		Leaves.	Digitalis.
	Apocynum cannabinum.		Root.	"
	Apocynum androsæmifolium.		Root.	"
Asclepiadaceæ . .	Hemidesmus indicus.		Root.	Saponin.
	Asclepias Cornuti.	(Milk weed.)	Rhizome.	Saponin and bitter.
	Asclepias incarnata.		Rhizome and roots.	Saponin and bitter.
	Asclepias tuberosa.		Root.	Saponin and bitter.
	Gonolobus Condurango.	Condurango.	Bark.	Astringent bitter.
Loganiaceæ . . .	Gelsemium sempervirens.	Gelsemium.	Root.	Gelsemin.
	Spigelia Marilandica.	Spigelia.	Rhizome and roots.	Anthelmintic.
	Strychnos Nux vomica.	Nux Vomica.	Seed and bark.	Strychnin.
	Strychnos Ignatia.	Semen Ignatiæ.	Seed.	"
Gentianeæ	Erythræa Centaurium.		Herb.	Aromatic bitter.
	Sabbatia angularis.		Herb.	" "
	Gentiana lutea.	Gentiana.	Root.	" "
	Gentiana puberula.		Root.	" "
	Swertia Chirata.	Chirata.	Herb.	" "
	Frasera Walteri.		Root.	" "
	Menyanthes trifoliata.		Leaves.	" "
Hydrophyllaceæ .	Eriodictyon glutinosum.	Yerba Santa.	Leaves.	Paralyzes taste endings.
Boragineæ	Symphytum officinale.		Root.	Demulcent.
	Alkanna tinctoria.		Root.	Dye.
Convolvulaceæ .	Ipomœa Jalapa.	Jalapa.	Tuberous root.	Anhydrid cathartic.
	Ipomœa orizabensis.		Tuberous root.	Anhydrid cathartic.
	Ipomœa simulans.		Tuberous root.	Anhydrid cathartic.
	Ipomœa pandurata.		Root.	Anhydrid cathartic.
	Convolvulus Mechoacanna.		Tuberous root.	Anhydrid cathartic.
	Convolvulus Scammonia.	Scammonium.	Gum resin.	Anhydrid cathartic.
Solanaceæ	Solanum Dulcamara.	Solanum.	Twigs.	Saponin.
	Solanum tuberosum.		Starch.	Starchy demulcent.
	Capsicum fastigiatum.	Capsicum.	Fruit.	Irritant (cantharidin).
	Atropa Belladonna.	Belladonna.	Roots and leaves.	Atropin.
	Datura Stramonium.	Stramonium.	Leaves and seed.	"
	Hyocyamus niger.		Leaves and seed.	"

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THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Solanaceæ	Duboisia myoporoides.		Leaves.	Atropin.
	Nicotina Tabacum.	Tabacum.	Leaves.	Nicotin.
Scrophularineæ .	Scrophularia nodosa.		Herb.	Bitter astringent.
	Chelone glabra.		Herb.	Bitter.
	Verbascum.	Mullein.	Leaves and flowers.	Demulcent.
	Digitalis purpurea.	Digitalis.	Leaves.	Digitalis.
	Veronica Virginica.	(Leptandra—Culver's root.)	Rhizome.	Anhydrid cathartics.
Orobanchaceæ . .	Epiphlegus Virginiana.	(Beech drop.)	Herb.	Bitter astringent.
Pedalineæ	Sesamum Indicum.		Fixed oil.	Oily emollients.
Labiatæ	Lavandula vera.	Lavandula.	Flowers.	Perfume.
	Collinsonia Canadensis.		Rhizome.	Bitter resin.
	Mentha piperita.		Herb.	Essential oils.
	Mentha viridis.		Herb.	" "
	Lycopus Virginicus.		Herb.	" "
	Cunila Mariana		Herb.	" "
	Origanum vulgare.		Herb.	" "
	Origanum Majarana.		Herb.	" "
	Thymus Serpyllum.	Thymus.	Herb.	" "
	Thymus vulgaris.		Leaves.	" "
	Hyssopus officinalis.		Herb.	" "
	Hedeoma pulegioides.		Herb.	" "
	Melissa officinalis.		Herb.	" "
	Saliva officinalis.		Leaves.	" "
	Rosmarinus officinalis.		Leaves.	" "
	Monarda punctata.		Herb.	" "
	Nepeta Cataria.		Herb.	" "
	Nepeta Glechoma.		Herb.	" "
	Scutellaria lateriflora.		Herb.	" "
	Marrubium vulgare.		Herb.	" "
	Leonurus Cardiaca.		Herb.	" "
Plantaginaceæ . .	Plantago major, etc.		Herb.	Bitter demulcent.
Chenopodiaceæ .	Chenopodium anthelminticum.	Chenopodium.	Fruit.	Anthelmintic.
	Beta Vulgaris.	Beet.	Sugar.	Saccharine demulcent.
Phytolaccaceæ . .	Phytolacca decandra.	Phytolacca (Poke).	Root and fruit.	Picrotoxin (Saponin ?).
Polyganaceæ . . .	Polygonum Bistorta.		Rhizome.	Tannin.
	Rheum officinale, etc.		Root.	Cathartin.
	Rheum rhaponticum, etc.	Rheum.	Root.	"
	Rumex crispus.		Root.	Tannin, bitter.
Aristolochiaceæ .	Asarum Canadense.		Rhizome.	Aromatic.
	Aristolochia Serpentaria, etc.	Serpentaria.	Rhizome and roots.	"

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[1] When the name of the drug is not given, it is identical with the generic name of the plant.

THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Piperaceæ	Piper angustifolium.		Leaves.	Irritants (carminatives).
	Piper Cubeba.	Cubeba.	Fruit.	Irritants (carminatives).
	Piper nigrum.		Fruit.	Irritants (carminatives).
	Piper methysticum.		Root.	Irritants (carminatives).
	Piper officinarum.		Fruit.	Irritants (carminatives).
Myristicaceæ . .	Myristica fragrans.	Myristica (Nutmeg).	Seed and fixed oil. Arillus (Macis).	Aromatic carminative.
Laurineæ	Cinnamomum Zeylanicum.	Cinnamomum.	Bark.	Aromatic carminative.
	Cinnamomum. Other species.		Bark.	Aromatic carminative.
	Cinnamomum Camphora.	Camphora.	Stearoptene.	Aromatic carminative.
	Nectandra Rodiæi.		Bark.	Aromatic carminative.
	Sassafras variifolium.	Sassafras.	Root, root bark, and pith.	Aromatic carminative.
	Laurus nobilis.		Leaves.	Aromatic carminative.
	Coto bark.	Coto.	Bark.	Astringent.
Thymelaceæ . . .	Daphne Merzereum, etc.	Mezereum.	Bark.	Irritants (cantharadin).
Santalaceæ	Santalum album.	Santalum.	Wood.	Essential oils.
Euphorbiaceæ . .	Euphorbia corollata.		Root.	Irritants (cantharidin).
	Euphorbia resinifera.	Euphorbium.	Exudation.	
	Jatropha, Hevea, etc., species.	Elastica (Caoutchouc).	Milk-juice.	Caoutchouc.
	Croton Tiglium.	Oleum Tiglii.	Seed and fixed oil.	Croton oil.
	Croton Eluteria.	Cascarilla.	Bark.	Bitter.
	Mallotus Philippinensis.	Kamala.	Glands.	Anthelmintic.
	Ricinus communis.	Oleum Ricicini.	Seed and fixed oil.	Oily cathartic.
	Stillingia sylvatica.	Stillingia.	Root.	Anthelmintic.
Urticaceæ	Ulmus fulva.	Ulmus.	Bark.	Gummy demulcent.
	Humulus Lupulus.	Humulus, Lupulinum.	Strobiles and glands.	Hypnotic, bitter.
	Cannabis sativa.	Cannabis Indica.	Herb, fruit, and fixed oil.	Hypnotic; seed, fatty and gummy demulcent.
	Morus rubra, etc.	(Mulberry.)	Fruit.	Laxative.
	Ficus Carica.	Fig.	Fruit.	"
	Ficus Indica.	Elastica.	Milk-juice.	Caoutchouc.
Juglandeæ	Juglans cinerea.	(Butternut.)	Bark.	Tannin.
	Juglans regia.	(Walnut.)	Fixed oil.	Fatty emollient.
Myricaceæ	Myrica cerifera.	(Bayberry Bark.)	Bark.	Saponin.
Cupuliferæ	Betula lenta.	(Beech.)	Volatile oil.	Essential oils; salicylic.
	Betula alba.		Tar.	Carbolic.

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[1] When the name of the drug is not given, it is identical with the generic name of the plant.

THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Cupuliferæ	Quercus alba.	(Oak.)	Bark.	Tannin.
	Quercus tinctoria.		Bark.	"
	Quercus infectoria.	Gallæ.	Galls.	"
	Castanea dentata.	(Chestnut.)	Leaves.	"
Salicaceæ	Salix alba, etc.	(Willow.)	Bark.	Tannin, salicylic.
Coniferæ.	Agathis Dammara.	Dammara.	Resin.	Turpentine, resin.
	Pinus Australis.		Oleoresin, resin, volatile oil, tar, empyreumatic, volatile oil.	Turpentine, resin.
	Larix Europæa.	(Larch.)	Oleoresin.	Turpentine, resin.
	Picea succinifera.		Resin, empyreumatic, volatile oil.	Turpentine, resin.
	Abies balsamea, etc.		Oleoresin.	Turpentine, resin.
	Abies pectinata.		Oleoresin.	Turpentine, resin.
	Abies Canadensis.	Pix Canadensis.	Oleoresin.	Turpentine, resin.
	Abies excelsa.		Oleoresin.	Turpentine, resin.
	Thuja occidentalis.	(Arbor Vitæ.)	Branchlets.	Turpentine, resin.
	Juniperus communis.		Fruit.	Turpentine, resin.
	Juniperus Oxycedrus.	Oleum Cadinum.	Tar.	Turpentine, resin.
	Juniperus Virginiana.		Branchlets.	Turpentine, resin.
	Juniperus Sabina.	(Savin.)	Branchlets.	Turpentine, resin.
Orchideæ	Vanilla planifolia.	Vanilla.	Fruit.	Perfume.
	Orchis mascula.	Salepa.	Tuber.	Starchy demulcents.
	Cypripedium pubescens, etc.	(Lady's slipper.)	Rhizome and roots.	Bitter.
Scitamineæ . . .	Maranta arundinacea.	(Arrow-root.)	Starch.	Starchy demulcents.
	Canna edulis.	(Cane-sugar.)	Starch.	Starchy demulcents.
	Curcuma leucorrhiza, etc.		Starch.	Starchy demulcents.
	Curcuma longa.	(Turmeric.)	Rhizome.	Dye, carminative.
	Curcuma Zedoaria.		Rhizome.	Carminative.
	Amomum Cardamomum, etc.	Cardamomum.	Fruit.	"
	Amomum Melegueta, etc.		Seed.	"
	Elettaria repens.	Cardamomum.	Fruit.	"
	Elettaria major.	Cardamomum.	Fruit.	"
	Zingiber officinale.	Zingiber.	Rhizome.	"
	Alpinia officinarum.	Galanga.	Rhizome.	"
Hæmodoraceæ .	Aletris farinosa.		Rhizome.	Bitter, starchy demulcent.

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THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Irideæ	Iris florentina.	(Orris.)	Rhizome.	Starchy demulcent, perfume.
	Iris versicolor.	(Blue flag.)	Rhizome and roots.	Anhydrid cathartic.
	Crocus sativus.	(Saffron.)	Stigma.	Dye, carminative.
Dioscoreaceæ . .	Dioscorea villosa.	(Wild yam.)	Rhizome.	Saponin.
Liliaceæ	Smilax medica, etc.	Sarsaparilla.	Root.	"
	Smilax ornata.		Root.	"
	Smilax China.		Rhizome.	"
	Polygonatum biflorum.	(Solomon's seal.)	Rhizome.	Digitalis.
	Convallaria majalis.	(Lily of the valley.)	Rhizome and roots.	"
	Aloe Socotrina, etc.	Aloe.	Inspissated juice.	Cathartic.
	Allium sativum.	(Garlic.)	Bulb.	Mustard.
	Urginea Scilla.	Scilla.	Bulb.	Digitalis.
	Colchicum autumnale.		Tuber and seed.	Colchicin.
	Chamælirium luteum.		Rhizome.	Sapotoxin.
	Trillium erectum.	(Wake robin.)	Rhizome.	"
	Veratrum album.		Rhizome and roots.	Veratrin.
	Veratrum viride.		Rhizome and roots.	"
	Asagræa officinalis.		Seed.	"
Palmæ	Areca Catechu.	Areca.	Seed.	Anthelmintic.
	Serenoa serrulata.	(Saw palmetto.)	Fruit.	Turpentine.
	Calamus Draco.	Draconis resina.	Resin.	Resin.
	Metraxylon Sagu, etc.	Sage.	Starch.	
	Elæis Guineensis.	Oleum Cocæ.	Fixed oil.	Fatty emollient.
	Cocos nucifera.	" "	Fixed oil.	Fatty emollient.
Aroideæ	Arisæma triphyllum.		Tuber.	Acrid volatile irritant.
	Arum maculatum.		Rhizome.	Acrid volatile irritant.
	Symplocarpus fœtidum.		Rhizome.	Acrid volatile irritant.
	Acorus Calamus.	Calamus.	Rhizome.	Carminative.
Gramineæ	Zea Mays.	Corn.	Stigma, starch, and fixed oil.	Demulcent.
	Oryza sativa.	(Rice.)	Starch.	
	Saccharum officinarum.		Sugar.	
	Andropogon muricatus.		Root.	Perfume.
	Andropogon Schœnanthus.		Volatile oil.	"
	Avena sativa.	(Oats.)	Meal.	
	Triticum vulgare.	(Wheat.)	Starch.	
	Agropyrum repens.	Triticum Repens.	Rhizome.	Demulcent.
	Hordeum distichum.	(Barley.)	Malt.	Nutrient, ferment.

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[1] When the name of the drug is not given, it is identical with the generic name of the plant.

THE CRUDE ORGANIC DRUGS BY ORDERS (OF VEGETABLE ORIGIN).—(*Continued.*)

ORDER.	ORIGIN.	DRUG.[1]	PART USED.	GROUP TO WHICH THE DRUG MAINLY BELONGS.
Lycopodiaceæ . .	Lycopodium clavatum.	Lycopodium.	Sporules.	Dusting powder.
Filices	Dryopteris Filix-mas, etc.	Filix Mas.	Rhizome.	Anthelmintic.
	Adiantum pedatum.	(Maiden hair.)		Astringent bitter.
	Cibotium Baromez.	Pengawahr.	Hairs.	Mechanical styptic.
Algæ	Chondrus crispus.	(Irish moss.)	Plant.	Gummy demulcent.
	Gigartina mammillosa.	" "	Plant.	Gummy demulcent.
	Fucus vesiculosus.	(Bladderwrack.)	Plant.	Gummy demulcent.
	Laminaria Cloustonia.	Laminaria.	Stipe.	Gummy demulcent.
Lichenes	Cetraria Islandica.	(Iceland moss.)	Plant.	Gummy demulcent.
Fungi	Polyporus officinalis.	Agaricus albus (Boletus Laricis).	Plant.	Anhidrotic, cathartic.
	Polyporus fomentarius.	Fungus Chirurgorum.	Plant.	Mechanical styptic.
	Ustilago Maydis.	(Corn smut.)	Plant.	Ergot.
	Claviceps purpurea.	Ergota.	Plant.	"
	Torula cerevisiæ.	(Yeast.)	Plant.	Ferment.

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[1] When the name of the drug is not given, it is identical with the generic name of the plant.

III.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]

(Adapted from U. S. Dispensatory and Coblentz's "Pharmacy.")

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Acetanilid	$C_6H_5NH.C_2H_3O$	194	5	0.2 to 1 Gm.	3 to 15 grs.
Acetic Ether	$C_2H_5.C_2H_3O_2$	8	a	0.6 to 1.9 c.c.	10 to 30 min.
Acetone	C_3H_6O	..	..	....	....
Acetophenone (hypnone)	C_8H_8O	..	..	....	....
Acid, Acetic	$HC_2H_3O_2$	a	a	....	....
" Arsenic	H_3AsO_4	2	..	....	....
" Arsenous	H_3AsO_3	80	141	0.001 to 0.004 Gm.	$\frac{1}{60}$ to $\frac{1}{16}$ gr.
" Benzoic	$HC_7H_5O_2$	500	2	0.65 to 1.9 Gm.	10 to 30 grs.
" Boric	H_3BO_3	25	15	0.65 to 1.9 Gm.	10 to 30 grs.
" Camphoric	$H_2C_{10}H_{14}O_4$	..	..	0.6 to 2 Gm.	10 to 30 grs.
" Carbolic	$C_6H_5.OH$	15	a	0.06 to 0.19 Gm.	1 to 3 grs.
" Carbonic	H_2CO_3	..	..	....	....
" Cinnamic	$HC_9H_7O_2$	..	..	....	....
" Citric	$H_3C_6H_5O_7 + H_2O$	0.63	1.61	0.65 to 1.9 Gm.	10 to 30 grs.
" Gallic	$HC_7H_5O_5 + H_2O$	100	5	0.33 to 1.9 Gm.	5 to 30 grs.
" Hydriodic	HI	a	a	....	....
" Hydrobromic (dilute)	HBr	a	a	1.9 to 7.4 c.c.	½ to 2 fl. drs.
" Hydrochloric (dilute)	HCl	a	a	0.6 to 1.9 c.c.	10 to 30 min.
" Hydrocyanic (dilute)	HCN	a	a	0.06 to 0.18 c.c.	1 to 3 min.
" Hydrofluoric	HF	a	a	....	....

Acid, Hypophosphorous (dilute)	HPH_2O_2	a	a	0.6 to 3.7 c.c.	10 to 60 min.
" Kinic (quinic)	$HC_7H_{11}O_6$	..	..	....	....
" Lactic	$HC_3H_5O_3$	a	a	1.9 to 7.4 c.c.	½ to 2 fl. drs.
" Meconic	$C_7H_4O_7$	sp.	v. s.	....	....
" Metaphosphoric	HPO_3	..	..	....	....
" Nitric (dilute)	HNO_3	a	a	0.3 to 1.9 c.c.	5 to 30 min.
" Nitrous	HNO_2	..	..	....	....
" Oleic	$HC_{18}H_{33}O_2$	ins.	a	....	....
" Oxalic	$H_2C_2O_4 + 2H_2O$	..	..	....	....
" Oxalic (dry)	$H_2C_2O_4$	8.17	6.8	....	....
" Palmitic	$HC_{16}H_{31}O_2$	..	..	....	....
" Phosphoric (dilute)	H_3PO_4	v. s.	v. s.	0.3 to 1.9 c.c.	5 to 30 min.
" Phosphorous	H_2PHO_3	..	..	....	....
" Picric	$C_6H_2(NO_2)_3OH$	86	s.	....	....
" Pyrophosphoric	$H_4P_2O_7$	..	..	....	....
" Salicylic	$HC_7H_5O_3$	450	2.4	0.65 to 1.6 Gm.	10 to 25 grs.
" Silicic	H_2SiO_3	..	..	....	....
" Stearic	$HC_{18}H_{35}O_2$	ins.	45	....	....
" Succinic	$H_2C_4H_4O_4$	19	8	....	....
" Sulphuric (dilute)	H_2SO_4	a	a	0.6 to 1.23 c.c.	10 to 20 min.
" Sulphurous	H_2SO_3	a	a	0.9 to 3.7 c.c.	¼ to 1 fl. dr.
" Tannic	$C_{14}H_{10}O_9$	1	0.6	0.2 to 0.65 Gm.	3 to 10 grs.
" Tartaric	$H_2C_4H_4O_6$	0.8	2.5	0.65 to 1.9 Gm.	10 to 30 grs.
" Titanic. See Titanic Oxid.					
" Trichloracetic	$HC_2Cl_3O_2$	..	..	....	....
" Tungstic. See Tungstic Oxid.					
" Uric	$C_5H_4N_4O_3$	..	..	....	....
" Valerianic	$HC_5H_9O_2$	30	a	0.2 to 0.5 Gm.	3 to 8 grs.
Aconitin	$C_{33}H_{43}NO_{12}$	150	5	....	....

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]—(*Continued.*)

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Alcohol, Amylic	$C_5H_{11}.OH$	sp.	a	....	....
" Ethylic	$C_2H_5.OH$	a	a	....	....
" Methylic	$CH_3.OH$	a	a	....	....
Aldehyd, Acetic	C_2H_4O	..	s.	....	....
" Formic	$CHO.H$	..	s.	....	....
Alum (Potash-Alum)	$Al_2(SO_4)_3 + K_2SO_4 + 24H_2O$	9	ins.	0.65 to 3.9 Gm.	10 to 60 grs.
" (dried)	$Al_2(SO_4)_3 + K_2SO_4$	20	ins.	0.3 to 1.9 Gm.	5 to 30 grs.
Aluminium	Al	ins.	ins.	....	....
" and Ammonium Sulphate	$Al_2(SO_4)_3 + (NH_4)_2SO_4 + 24H_2O$	s.	..	....	....
" Hydrate	$Al_2(OH)_6$	ins.	ins.	0.06 to 0.65 Gm.	1 to 10 grs.
" Sulphate	$Al_2(SO_4)_3 + 16H_2O$	1.2	ins.	....	....
Ammonia	NH_3	a	a	....	....
Ammoniated Mercury. See Mercur-Ammo	nium Chlorid.				
Ammonio-Ferric Sulphate (Iron-Alum)	$Fe_2(SO_4)_3 + (NH_4)_2SO_4 + 24H_2O$	s.	..	....	....
Ammonium Acetate	$NH_4C_2H_3O_2$	v. s.	..	....	....
" Arsenite (metarsenite)	NH_4AsO_2	..	..	....	....
" Benzoate	$NH_4C_7H_5O_2$	5	28	0.65 to 1.9 Gm.	10 to 30 grs.
" Bromid	NH_4Br	1.5	30	0.65 to 3.9 Gm.	10 to 60 grs.
" Carbonate (official)	$NH_4HCO_3.NH_4NH_2CO_2$	4	dec.	0.3 to 0.97 Gm.	5 to 15 grs.
" Carbonate (pure)	$(NH_4)_2CO_3$	..	..	....	....
" Chlorid	NH_4Cl	3	sp.	0.3 to 1.9 Gm.	5 to 30 grs.
" Citrate	$(NH_4)_3C_6H_5O_7$	s.	..	....	....
" Iodid	NH_4I	1	9	0.19 to 0.65 Gm.	3 to 10 grs.
" Lactate	$NH_4C_3H_5O_3$	s.	..	....	....

Ammonium Molybdate	$(NH_4)_2MoO_4$	..	..	....	....
" Nitrate	NH_4NO_3	0.5	20	0.65 to 1.9 Gm.	10 to 30 grs.
" Oxalate	$(NH_4)_2C_2O_4 + H_2O$	3	..	....	....
" Persulphate	$(NH_4)_2S_2O_8$	s.	..	....	....
" Phosphate	$(NH_4)_2HPO_4$	4	ins.	....	....
" Salicylate	$NH_4C_7H_5O_3$	s.	..	....	....
" Sulphate	$(NH_4)_2SO_4$	1.3	sp.	....	....
" Sulphhydrate	NH_4HS	s.	..	....	....
" Sulphid	$(NH_4)_2S$	s.	..	....	....
" Tartrate	$(NH_4)_2C_4H_4O_6$	s.	..	....	....
" Valerianate	$NH_4C_5H_9O_2$	v. s.	v. s.	0.13 to 0.5 Gm.	2 to 8 grs.
Amyl Acetate	$C_5H_{11}C_2H_3O_2$	ins.	a	....	....
" Nitrite	$C_5H_{11}NO_2$	ins.	a	0.12 to 0.25 c.c.	2 to 4 min.
Amylene (pentene)	C_5H_{10}	..	..	0.6 to 2 Gm.	10 to 30 grs.
Antimonous Chlorid	$SbCl_3$	..	..	....	....
" Oxid	Sb_2O_3	n. ins.	ins.	0.065 to 0.19 Gm.	1 to 3 grs.
" Sulphid	Sb_2S_3	ins.	ins.	....	....
Antimony	Sb	ins.	ins.	....	....
" and Potassium Tartrate (dry)	$K(SbO)C_4H_4O_6$	17	ins.	0.008 to 0.19 Gm.	⅛ to 3 grs.
Antimonyl Potassium Tartrate	$2KSbOC_4H_4O_6 + H_2O$	..	..	....	....
Antipyrin. See Phenazone.					
Apomorphin	$C_{17}H_{17}NO_2$	..	..	....	....
" Hydrochlorate	$C_{17}H_{17}NO_2HCl$	6.8	25	0.004 to 0.008 Gm.	$\frac{1}{16}$ to ⅛ gr.
Arabin	$2C_6H_{10}O_5 + H_2O$	..	..	....	....
Arsenic	As	ins.	ins.	....	....
" Oxid	As_2O_5	..	..	....	....
" Sulphid	As_2S_5	..	..	....	....
Arsenous Iodid	AsI_3	3.5	10	0.001 to 0.006 Gm.	$\frac{1}{60}$ to $\frac{1}{10}$ gr.
" Oxid	As_2O_3	..	..	....	....

Abbreviations: s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]—(*Continued.*)

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Arsenous Sulphid	As_2S_3	..	..	....	....
Atropin	$C_{17}H_{23}NO_3$	..	..	0.0006 to 0.001 Gm.	$\frac{1}{96}$ to $\frac{1}{64}$ gr.
" Sulphate	$(C_{17}H_{23}NO_3)_2H_2SO_4$	0.4	6.2	0.0006 to 0.001 Gm.	$\frac{1}{96}$ to $\frac{1}{48}$ gr.
Barium	Ba	ins.	ins.	....	....
" Carbonate	$BaCO_3$	ins.	n. ins.	....	....
" Chlorid	$BaCl_2 + 2H_2O$	2½	ins.	....	....
" Hydrate	$Ba(OH)_2$	n. ins.	..	....	....
" Nitrate	$Ba(NO_3)_2$	8–12	ins.	....	....
" Peroxid	BaO_2	..	..	....	....
" Sulphate	$BaSO_4$	ins.	..	....	....
Benzanilid	$C_{13}H_{11}NO$	n. ins.	58	0.3 to 1 Gm.	5 to 15 grs.
Benzene (Benzol)	C_6H_6	ins.	..	....	....
Benzoic Aldehyd	C_7H_6O	..	..	....	....
Benzyl Alcohol	$C_7H_7.OH$	..	..	....	....
Beryllium	Be	..	..	....	....
Bismuth	Bi	ins.	ins.	....	....
" Carbonate (basic)	$(BiO)_2CO_3 + H_2O$	ins.	ins.	0.6 to 4 Gm.	10 to 60 grs.
" Carbonate (normal)	$Bi_2(CO_3)_3$	..	..	....	....
" Citrate	$BiC_6H_5O_7$	ins.	ins.	0.3 to 1 Gm.	5 to 15 grs.
" Oxychlorid	BiOCl	..	..	....	....
" Oxyiodid	BiOI	ins.	ins.	....	....
" Subnitrate	$BiONO_3 + H_2O$	ins.	ins.	0.65 to 3.9 Gm.	10 to 60 grs.
Boron	B	ins.	ins.	....	....
" Trioxid	B_2O_3	..	..	....	....

Bromin	Br	30	s (dec.)	....	....
Brucin	$C_{23}H_{26}N_2O_4 + 4H_2O$	750	2	0.05 Gm.	1 gr.
" (dry)	$C_{23}H_{26}N_2O_4$	..	..	....	....
Cadmium	Cd	..	..	....	....
" Iodid	CdI_2	2	sol.	....	....
" Sulphate	$CdSO_4$	v. s.	v. s.	....	....
Cæsium	Cs	..	..	....	....
Caffein	$C_8H_{10}N_4O_2 + H_2O$	80	33	0.065 to 0.19 Gm.	1 to 3 grs.
Calcium	Ca	ins.	ins.	....	....
" Acetate	$Ca(C_2H_3O_2)_2$	s.	s.	....	....
" Bromid	$CaBr_2$	0.7	1	0.65 to 3.9 Gm.	10 to 60 grs.
" Carbonate	$CaCO_3$	ins.	ins.	0.3 to 3.9 Gm.	5 to 60 grs.
" Chlorid	$CaCl_2$	1½	8	0.3 to 1.3 Gm.	5 to 20 grs.
" Chlorid (crystallized)	$CaCl_2 + 6H_2O$	..	..	....	....
" Hydrate	$Ca(OH)_2$	sp.	..	....	....
" Hypochlorite	$Ca(OCl)_2$	..	..	....	....
" Hypophosphite	$CaH_4(PO_2)_2$	6.8	ins.	0.3 to 1.9 Gm.	5 to 30 grs.
" Oxalate	CaC_2O_4	ins.	ins.	....	....
" Oxid	CaO	dec.	..	....	....
" Phosphate	$Ca_3(PO_4)_2$	ins.	ins.	0.32 to 1.9 Gm.	5 to 30 grs.
" Sulphate	$CaSO_4$	382	ins.	....	....
" Sulphate (crystallized)	$CaSO_4 + 2H_2O$	..	..	....	....
" Sulphid (monosulphid)	CaS	s.	..	....	....
" Tartrate	$CaC_4H_4O_6$	..	..	....	....
Calomel. See Mercurous Chlorid.					
Camphor	$C_{10}H_{16}O$	sp.	v. s.	0.25 to 0.6 Gm.	1 to 10 grs.
" Monobromated	$C_{10}H_{15}BrO$	n. ins.	6	0.065 to 0.32 Gm.	1 to 5 grs.
Carbon	C	ins.	ins.	....	....
" Dioxid	CO_2	s.	s.	....	....

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]—(*Continued.*)

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Carbon Disulphid	CS_2	535	v s.	0.3 to 0.6 c.c	5 to 10 gtt.
Cerium	Ce	ins.	ins.	....	....
" Oxalate	$Ce_2(C_2O_4)_3 + 9H_2O$	ins.	ins.	....	....
" Oxalate (dry)	$Ce_2(C_2O_4)_3$	ins.	ins.	....	....
Chloral, Anhydrous	C_2HCl_3O	v. s.	v. s.	....	....
" Hydrate	$C_2HCl_3O + H_2O$	v. s.	v. s.	0.65 to 2.9 Gm.	10 to 45 grs.
Chloralamid	$C_3H_4Cl_3NO_2$	..	..	0.3 to 2 Gm.	5 to 30 grs,
Chlorin	Cl	v. s.	..	....	....
Chloroform	$CHCl_3$	200	a	0.18 to 0.31 c.c.	2 to 5 min,
Chrome-alum	$Cr_2(SO_4)_3 + K_2SO_4 + 24H_2O$	s.	..	....	....
Chromium	Cr	ins.	ins.	....	....
" Sesquioxid	Cr_2O_3	s.	..	....	....
" Trioxid	CrO_3	v. s.	v. s.	....	....
Cinchonidin	$C_{19}H_{22}N_2O$	2500	20	....	....
" Sulphate	$(C_{19}H_{22}N_2O)_2H_2SO_4 + 3H_2O$	70	66	0.19 to 1.9 Gm.	3 to 30 grs.
" Sulphate (dry)	$(C_{19}H_{22}N_2O)_2H_2SO_4$	s.	s.	....	....
Cinchonin	$C_{19}H_{22}N_2O$	3760	116	0.065 to 1.8 Gm.	1 to 30 grs.
" Sulphate	$(C_{19}H_{22}N_2O)_2H_2SO_4 + 2H_2O$	66	10	0.065 to 1.8 Gm.	1 to 30 grs.
" Sulphate (dry)	$(C_{19}H_{22}N_2O)_2H_2SO_4$	s.	s.	....	....
Cinnabar. See Mercuric Sulphid.					
Cobalt	Co	ins.	ins.	....	....
Cobaltous Nitrate	$Co(NO_3)_2 + 6H_2O$	s.	..	....	....
Cocain	$C_{17}H_{21}NO_4$	700	v. s.	....	....
" Hydrochlorate	$C_{17}H_{21}NO_4HCl$	0.48	3.5	0.008 to 1.3 Gm.	⅛ to 2 grs.

Codein	$C_{18}H_{21}NO_3 + H_2O$	80	3	0.02 to 1.9 Gm.	¼ to 3 grs.
Columbium. See Niobium.					
Coniin	$C_8H_{17}N$	100	v. s.	0.002 to 0.003 Gm.	1/30 to 1/20 gr.
Copper	Cu	ins.	ins.	....	....
" Acetate	$Cu(C_2H_3O_2)_2 + H_2O$	15	16	....	....
" Acetate (basic)	$Cu(C_2H_3O_2)_2 + CuO + 6H_2O$	. .	. .	....	....
" Carbonate (basic)	$CuCO_3 + Cu(OH)_2$	n. ins.	. .	....	....
" Sulphate	$CuSO_4 + 5H_2O$	2.6	n. ins.	0.03 to 0.65 Gm.	½ to 10 grs.
" Sulphate (ammoniacal)	$CuSO_4 + 4NH_3 + H_2O$	s.	s.	....	....
Corrosive Sublimate. See Mercuric Chlorid.					
Cresol (cresylic acid)	C_7H_8O	sp.	s.	....	....
Cupric Oxid	CuO	ins.	ins.	....	....
" Sulphate. See Copper Sulphate.					
" Sulphate (dry)	$CuSO_4$	s.	s.	....	....
" Tartrate	$CuC_4H_4O_6 + 3H_2O$	s.	s.	....	....
Cuprous Oxid	Cu_2O	ins.	ins.	....	....
Cyanogen	$(CN)_2$	dec.	. .	....	....
Didymium	Di	. .	. .	....	....
Diethylsulphon-Dimethylmethane (sulphonal)	$C_7H_{16}S_2O_4$	500	65	0.3 to 1 Gm.	5 to 15 grs.
Diiodparaphenol Sulphonic Acid (soziodol)	$C_6H_4I_2SO_4$	. .	. .	....	....
Dimethyl Phenyl-Pyrazolon (antipyrin)	$C_{11}H_{12}N_2O$	1	1	0.3 to 1 Gm.	5 to 15 grs.
Diphenylamin	$(C_6H_5)_2NH$	. .	. .	....	....
Dithymol Diiodid (aristol)	$C_{20}H_{24}O_2I_2$	ins.	sp.	....	....
Elaterin	$C_{20}H_{28}O_5$	4250	337	0.003 to 0.005 Gm.	1/20 to 1/12 gr.
Erbium	E	. .	. .	....	....
Ether, Ethylic (common sulphuric)	$(C_2H_5)_2O$	12	a	....	....
Ethyl Acetate. See Acetic Ether.		8	a	....	....
" Bromid	C_2H_5Br	sp.	a	....	....
" Carbamate (urethane)	$C_3H_7NO_2$	v. s.	v. s.	0.3 to 3 Gm.	5 to 50 grs.

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]—(*Continued.*)

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Ethyl Chlorid	C_2H_5Cl	..	a	....	....
" Nitrite	$C_2H_5NO_2$	sp. s.	a	....	....
Ethylene	C_2H_4	..	..	....	....
Eucalyptol	$C_{10}H_{18}O$	n. ins.	a	0.3 to 1.85 c.c.	5 to 30 min.
Eugenol	$C_{10}H_{12}O_2$	sp.	v. s.	....	....
Exalgin (methyl acetanilid)	$C_9H_{11}NO$	..	..	0.3 to 1 Gm.	5 to 15 grs.
Ferric Acetate	$Fe_2(C_2H_3O_2)_6$	4	s.	....	....
" Ammonium Sulphate	$Fe_2(NH_4)_2(SO_4)_4 + 24H_2O$	3	ins.	0.3 to 0.97 Gm.	5 to 15 grs.
" Ammonium Sulphate (dry)	$Fe_2(NH_4)_2(SO_4)_4$	s.	ins.	....	....
" Chlorid	$Fe_2Cl_6 + 12H_2O$	v. s.	v. s.	0.065 to 0.79 Gm.	1 to 3 grs.
" Chlorid (dry)	Fe_2Cl_6	v. s.	v. s.	....	....
" Citrate	$Fe_2(C_6H_5O_7)_2 + 6H_2O$	s.	ins.	0.3 to 0.97 Gm.	5 to 15 grs.
" Hydrate	$Fe_2(OH)_6$	ins.	ins.	3.9 to 15.5 Gm.	1 to 4 drs.
" Hypophosphite	$Fe_2(H_2PO_2)_6$	n. ins.	..	0.3 to 0.65 Gm.	5 to 10 grs.
" Nitrate	$Fe_2(NO_3)_6$	s.	s.	....	....
" Oxid (sesquioxid)	Fe_2O_3	ins.	ins.	....	....
" Phosphate	$Fe_2(PO_4)_2$	v. s.	ins.	0.3 to 0.65 Gm.	5 to 10 grs.
" Pyrophosphate	$(Fe_2)_2(P_2O_7)_3$	v. s.	ins.	0.13 to 0.3 Gm.	2 to 5 grs.
" Sulphate (basic)	$Fe_4O(SO_4)_5$	s.	ins.	....	....
" Sulphate (normal)	$Fe_2(SO_4)_3$	s.	ins.	....	....
Ferricyanic Acid	$H_6Fe_2(CN)_{12}$	..	..	....	....
Ferrocyanic Acid	$H_4Fe(CN)_6$	..	..	....	....
Ferrous Bromid	$FeBr_2$	s.	s.	....	....
" Carbonate	$FeCO_3$	sp.	ins.	0.13 to 0.65 Gm.	2 to 10 grs.

Ferrous Hydrate	$Fe(OH)_2$	ins.	ins.	....	....
" Iodid	FeI_2	s.	s.	0.3 to 0.97 Gm.	5 to 15 grs.
" Lactate	$Fe(C_3H_5O_3)_2 + 3H_2O$	40	ins.	0.065 to 0.32 Gm.	1 to 5 grs.
" Oxalate	$FeC_2O_4 + H_2O$	n. ins.	ins.	....	....
" Oxid	FeO	ins.	ins.	....	....
" Sulphate	$FeSO_4 + 7H_2O$	s.	ins.	0.65 to 0.3 Gm.	1 to 5 grs.
" Sulphate (anhydrous)	$FeSO_4$	s.	ins.	....	....
" Sulphate (dried)	$FeSO_4 + H_2O$	1.8	ins.	0.3 to 0.19 Gm.	$\frac{1}{2}$ to 3 grs.
" Sulphid	FeS	ins.	ins.	....	....
Fluorin	F	..	..	....	....
Gallium	Ga	..	..	....	....
Glucid (saccharin)	$C_7H_5SO_3N$	sp.	..	....	....
Glucinum. See Beryllium.					
Glucose	$C_6H_{12}O_6$	s.	sp.	....	....
Glycerin	$C_3H_5(OH)_3$	a	a	0.3 to 3.7 c.c.	5 to 60 min.
Glyceryl Trinitrate (nitroglycerin)	$C_3H_5(NO_3)_3$	sp.	s.	....	....
Glycol	$C_2H_4(OH)_2$	..	..	....	....
Gold	Au	ins.	ins.	....	....
" and Sodium Chlorid	$AuCl_3 + NaCl$	2	sp.	0.002 to 0.006 Gm.	$\frac{1}{30}$ to $\frac{1}{10}$ gr.
" Chlorid	$AuCl_3$	s.	s.	....	....
Grape-sugar. See Glucose.					
Guaiacol	$C_7H_8O_2$	200	a	0.3 to 2 Gm.	5 to 30 grs.
Homatropin	$C_{16}H_{21}NO_3$	sp.	s.	....	....
Hydrastinin Hydrochlorate	$C_{11}H_{11}NO_2HCl$	0.3	3	0.025 Gm.	$\frac{1}{3}$ gr.
Hydrogen	H	..	..	....	....
" Dioxid	H_2O_2	a	a	....	....
" Oxid (water)	H_2O	..	..	....	....
" Sulphid	H_2S	s.	s.	....	....
Hydroquinone	$C_6H_6O_2$	20	v. s.	....	....

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]—(*Continued.*)

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Hyoscin Hydrobromate	$C_{17}H_{21}NO_4HBr + 3H_2O$	0.3	2	0.0002 to 0.0006 Gm.	$\frac{1}{150}$ to $\frac{1}{100}$ gr.
" Hydrobromate (dry)	$C_{17}H_{21}NO_4HBr$	s.	s.	....	....
Hyoscyamin	$C_{17}H_{23}NO_3$	500	v. s.	....	....
" Hydrobromate	$C_{17}H_{23}NO_3HBr$	0.3	2	....	....
" Sulphate	$(C_{17}H_{23}NO_3)_2H_2SO_4$	0.5	0.5	0.001 to 0.002 Gm.	$\frac{1}{64}$ to $\frac{1}{32}$ gr.
Indigo-blue	C_8H_5NO	. .	. .	....	....
Indium	In	. .	. .	....	....
Iodin	I	5000	10	0.02 to 0.065 Gm.	¼ to 1 gr.
Iodoform	CHI_3	n. ins.	52	0.03 to 0.19 Gm.	½ to 3 grs.
Iodol (tetraiodopyrrol)	C_4HI_4N	5000	3	....	....
Iridium	Ir	. .	. .	....	....
Iron	Fe	ins.	ins.	....	....
" Compounds. See Ferrous and Ferric.					
Lactose. See Sugar of Milk.					
Lanthanum	La	. .	. .	....	....
Lead	Pb	ins.	ins.	....	....
" Acetate	$Pb(C_2H_3O_2)_2 + 3H_2O$	2.3	21	0.065 to 0.3 Gm.	1 to 5 grs.
" Acetate (basic)	$Pb_2O(C_2H_3O_2)_2$	s.	s.	....	....
" Acetate (dry)	$Pb(C_2H_3O_2)_2$	s.	s.	....	....
" Carbonate (official)	$2(PbCO_3) + Pb(OH)_2$	ins.	ins.	....	....
" Carbonate (pure)	$PbCO_3$	ins.	ins.	....	....
" Dioxid	PbO_2	n. ins.	n. ins.	....	....
" Iodid	PbI_2	2000	sp.	0.02 to 0.065 Gm.	¼ to 1 gr.
" Nitrate	$Pb(NO_3)_2$	2	n. ins.	0.02 to 0.03 Gm.	¼ to ½ gr.

Lead Oxid	PbO	n. ins.	ins.	....	....
" Red Oxid of	Pb_3O_4	ins.	ins.	....	....
Lime. See Calcium Oxid.					
Lithium	Li	dec.	dec.	....	....
" Benzoate	$LiC_7H_5O_2$	4	12	0.65 to 1.9 Gm.	10 to 30 grs.
" Bromid	$LiBr$	0.6	v. s.	0.3 to 1.9 Gm.	5 to 30 grs.
" Carbonate	Li_2CO_3	80	ins.	0.19 to 0.97 Gm.	3 to 15 grs.
" Citrate	$Li_3C_6H_5O_7$	2	n. ins.	0.65 to 1.9 Gm.	10 to 30 grs.
" Salicylate	$LiC_7H_5O_3$	v. s.	v. s.	0.65 to 1.9 Gm.	10 to 30 grs.
Magnesium	Mg	ins.	ins.	....	....
" Carbonate (official)	$(MgCO_3)_4.Mg(OH)_2 + 5H_2O$	n. ins.	ins.	3.9 to 11.6 Gm.	1 to 3 drs.
" Carbonate (pure)	$MgCO_3$	n. ins.	ins.	....	....
" Oxid (magnesia)	MgO	n. ins.	ins.	....	....
" Sulphate	$MgSO_4 + 7H_2O$	1.5	ins.	15.5 to 46.6 Gm.	½ to 1½ ozs.
" Sulphate (dry)	$MgSO_4$	s.	ins.	....	....
" Sulphite	$MgSO_3 + 6H_2O$	40	ins.	....	....
Manganese	Mn	ins.	ins.	....	....
" Dioxid	MnO_2	ins.	ins.	0.19 to 0.97 Gm.	3 to 15 grs.
Manganous Sulphate	$MnSO_4 + 4H_2O$	0.8	ins.	0.3 to 0.97 Gm.	5 to 15 grs.
Menthol	$C_{10}H_{19}OH$	sl.	v. s.	0.065 to 0.32 Gm.	1 to 5 grs.
Mercur-Ammonium Chlorid	NH_2HgCl	ins.	ins.	....	....
Mercuric Chlorid	$HgCl_2$	16	3	0.002 to 0.008 Gm.	$\frac{1}{32}$ to $\frac{1}{8}$ gr.
" Cyanid	$Hg(CN)_2$	12.8	15	0.002 to 0.008 Gm.	$\frac{1}{24}$ to $\frac{1}{8}$ gr.
" Iodid	HgI_2	n. ins.	sp.	0.004 to 0.02 Gm.	$\frac{1}{16}$ to $\frac{1}{8}$ gr.
" Nitrate	$Hg(NO_3)_2$	s.	..	....	....
" Oxid	HgO	ins.	ins.	....	....
" Potassium Iodid	$HgI_2 + 2KI$	s.	..	....	....
" Sulphate (normal)	$HgSO_4$	..	..	....	....
" Sulphate (yellow or basic)	$Hg(HgO)_2SO_4$	2000	ins.	....	....

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]—(*Continued.*)

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Mercuric Sulphid	HgS	ins.	ins.	....	....
Mercurous Chlorid	Hg_2Cl_2	ins.	ins.	0.065 to 0.97 Gm.	1 to 15 grs.
" Iodid	Hg_2I_2	ins.	ins.	0.03 to 0.19 Gm.	½ to 3 grs.
" Nitrate	$Hg_2(NO_3)_2$	..	..	....	....
" Sulphate	Hg_2SO_4	..	..	....	....
Mercury	Hg	ins.	ins.	....	....
Methyl Alcohol. See Alcohol, Methylic.					
" Iodid	CH_3I	..	..	....	....
" Salicylate	$CH_3C_7H_5O_3$	sp.	a	0.06 to 0.3 c c.	1 to 5 min.
Methylene Chlorid	CH_2Cl_2	..	..	....	....
Molybdenum	Mo	ins.	ins.	....	....
Molybdic Oxid	MoO_3	..	..	....	....
Morphin	$C_{17}H_{19}NO_3 + H_2O$	4350	300	0.004 to 0.016 Gm.	$\frac{1}{16}$ to $\frac{1}{4}$ gr.
" (dry)	$C_{17}H_{19}NO_3$	..	..	....	....
" Acetate	$C_{17}H_{19}NO_3.HC_2H_3O_2 + 3H_2O$	2.5	47.6	0.004 to 0.02 Gm.	$\frac{1}{16}$ to $\frac{1}{4}$ gr.
" Hydrochlorate	$C_{17}H_{19}NO_3HCl + 3H_2O$	24	62	0.005 to 0.03 Gm.	$\frac{1}{12}$ to $\frac{1}{2}$ gr.
" Hydrochlorate (dry)	$C_{17}H_{19}NO_3HCl$	..	..	....	....
" Sulphate	$(C_{17}H_{19}NO_3)_2H_2SO_4 + 5H_2O$	21	702	0.005 to 0.03 Gm.	$\frac{1}{12}$ to $\frac{1}{2}$ gr.
" Sulphate (dry)	$(C_{17}H_{19}NO_3)_2H_2SO_4$	..	..	....	....
Naphtalin	$C_{10}H_8$	ins.	15	0.13 to 0.65 Gm.	2 to 10 grs.
Naphtol	$C_{10}H_7(OH)$	1000	0.75	0.13 to 0.97 Gm.	2 to 15 grs.
Narcein	$C_{23}H_{29}NO_9$	1200	800	....	....
Narcotin	$C_{22}H_{23}NO_7$	n. ins.	80	....	....
Nickel	Ni	ins.	ins.	....	....

Nicotin	$C_{10}H_{14}N_2$	s.	v. s.	....	....
Niobium	Nb	..	..	....	....
Nitrogen	N	..	..	....	....
" Dioxid	NO	..	..	....	....
Osmium	Os	ins.	ins.	....	....
Oxygen	O	..	..	....	....
Palladium	Pd	ins.	ins.	....	....
Paraldehyd	$C_6H_{12}O_3$	8.5	a	0.3 to 1 Gm.	5 to 15 grs.
Paramorphin. See Thebain.					
Phenacetin	$C_{10}H_{13}NO_2$	sp. s.	16	0.3 to 1 Gm.	5 to 15 grs.
Phenazone (antipyrin)	$C_{11}H_{12}N_2O$	1	1	0.3 to 1 Gm.	5 to 15 grs.
Phenol. See Carbolic Acid.					
Phosphorus	P	ins.	s.	0.0006 to 0.003 Gm.	$\frac{1}{100}$ to $\frac{1}{20}$ gr.
" Oxychlorid	$POCl_3$	..	..	....	....
" Pentachlorid	PCl_5	..	..	....	....
" Trichlorid	PCl_3	..	..	....	....
Physostigmin Salicylate	$C_{15}H_{21}N_3O_2C_7H_6O_3$	130	12	0.0006 to 0.002 Gm.	$\frac{1}{100}$ to $\frac{1}{30}$ gr.
Picrotoxin	$C_{30}H_{34}O_{13}$	240	9	0.0005 to 0.001 Gm.	$\frac{1}{120}$ to $\frac{1}{60}$ gr.
Pilocarpin Hydrochlorate	$C_{11}H_{16}N_2O_2HCl$	v. s.	v. s.	0.008 to 0.03 Gm.	$\frac{1}{8}$ to $\frac{1}{2}$ gr.
Piperazin	$C_4H_{10}N_2$	v. s.	..	....	....
Piperin	$C_{17}H_{19}NO_3$	n. ins.	30	0.065 to 0.65 Gm.	1 to 10 grs.
Platinic Chlorid	$PtCl_4$	s.	..	....	....
Platinum	Pt	ins.	ins.	....	....
Potassium	K	dec.	..	....	....
" Acetate	$KC_2H_3O_2$	0.36	1.9	0.65 to 3.9 Gm.	10 to 60 grs.
" Acid Carbonate	$KHCO_3$	v. s.	ins.	....	....
" Acid Oxalate (salt of sorrel)	KHC_2O_4	s.	ins.	....	....
" and Sodium Tartrate	$KNaC_4H_4O_6 + 4H_2O$	1.4	n. ins.	2 to 8 Gm.	½ to 2 drachms
" Arsenite (metarsenite)	$KAsO_2$	v. s.	sp.	....	....

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]—(*Continued.*)

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Potassium Bichromate	$K_2Cr_2O_7$	10	ins.	0.006 to 0.06 Gm.	$\frac{1}{16}$ to 1 gr.
" Bitartrate	$KHC_4H_4O_6$	201	sp.	3.9 to 31 Gm.	1 to 8 drs.
" Bromid	KBr	1.6	200	0.65 to 3.9 Gm.	10 to 60 grs.
" Carbonate	$(K_2CO_3)_2 3H_2O$	1.1	ins.	0.65 to 1.9 Gm.	10 to 30 grs.
" Chlorate	$KClO_3$	16.7	sp.	0.32 to 1.3 Gm.	5 to 20 grs.
" Chlorid	KCl	3	s.	....	....
" Chromate	K_2CrO_4	s.	..	....	....
" Citrate	$K_3C_6H_5O_7 + H_2O$	0.6	sp.	0.97 to 3.9 Gm.	15 to 60 grs.
" Cyanid	KCN	2	sp.	0.008 to 0.01 Gm.	$\frac{1}{8}$ to $\frac{1}{6}$ gr.
" Ferricyanid	$K_3Fe(CN)_6$	4	sp.	....	....
" Ferrocyanid	$K_4Fe(CN)_6 + 3H_2O$	4	ins.	....	....
" Hydrate	KOH	0.5	2	....	....
" Hypophosphite	KH_2PO_2	0.6	7.3	0.32 to 1.9 Gm.	5 to 30 grs.
" Iodid	KI	0.75	18	0.32 to 3.9 Gm.	5 to 60 grs.
" Nitrate	KNO_3	3.8	sp.	0.65 to 1.9 Gm.	10 to 30 grs.
" Permanganate	$KMnO_4$	16	dec.	0.03 to 0.19 Gm.	$\frac{1}{2}$ to 3 grs.
" Sulphate	K_2SO_4	9.5	ins.	1.9 to 15.5 Gm.	$\frac{1}{2}$ to 4 drs.
" Sulphite	$K_2SO_3 + 2H_2O$	s.	..	....	....
" Sulphocyanate	$KSCN$	s.	..	....	....
" Tartrate	$(K_2C_4H_4O_6)_2 + H_2O$	1	ins.	....	....
Prussian Blue (ferric ferrocyanid)	$Fe_4(Fe(CN)_6)_3$	n. ins.	ins.	....	....
Prussic Acid. See Acid, Hydrocyanic.					
Pyridin	C_5H_5N	s.	v. s.	....	....

Pyrogallol (pyrogallic acid)	$C_6H_3(OH)_3$	1.7	1	....	....
Pyrrol	C_4H_5N	..	..	....	....
Quinidin	$C_{20}H_{24}N_2O_2$	2000	20	....	....
" Sulphate	$(C_{20}H_{24}N_2O_2)_2H_2SO_4 + 2H_2O$	100	8	0.065 to 1.9 Gm.	1 to 30 grs.
" Sulphate (dry)	$(C_{20}H_{24}N_2O_2)_2H_2SO_4$	s.	s.	....	....
Quinin	$C_{20}H_{24}N_2O_2 + 3H_2O$	1670	6	....	....
" (dry)	$C_{20}H_{24}N_2O_2$	n. ins.	s.	....	....
" Bisulphate	$(C_{20}H_{24}N_2O_2)H_2SO_4 + 7H_2O$	10	32	0.06 to 1.9 Gm.	1 to 30 grs.
" Bisulphate (dry)	$C_{20}H_{24}N_2O_2H_2SO_4$	s.	s.	....	..?.
" Hydrobromate	$C_{20}H_{24}N_2O_2HBr + H_2O$	54	0.6	0.06 to 1.9 Gm.	1 to 30 grs.
" Hydrobromate (dry)	$C_{20}H_{24}N_2O_2HBr$	s.	s.	....	....
" Hydrochlorate	$C_{20}H_{24}N_2O_2HCl + 2H_2O$	34	3	0.06 to 1.9 Gm.	1 to 30 grs.
" Hydrochlorate (dry)	$C_{20}H_{24}N_2O_2HCl$	s.	s.	....	....
" Sulphate	$(C_{20}H_{24}N_2O_2)_2H_2SO_4 + 7H_2O$	740	65	0.06 to 1.9 Gm.	1 to 30 grs.
" Sulphate (dry)	$(C_{20}H_{24}N_2O_2)_2H_2SO_4$	s.	s.	....	....
" Valerianate	$C_{20}H_{24}N_2O_2C_5H_{10}O_2 + H_2O$	100	5	0.06 to 1.9 Gm.	1 to 30 grs.
Quinolin	C_9H_7N	s.	v. s.	....	....
Resorcin	$C_6H_6O_2$	0.6	0.5	0.19 to 0.65 Gm.	3 to 10 grs.
Rhodium	Rh	..	..	....	....
Rubidium	Rb	..	..	....	....
Ruthenium	Ru	..	.	....	....
Salicin	$C_{13}H_{18}O_7$	28	30	0.65 to 1.9 Gm.	10 to 30 grs.
Salol (phenyl salicylate)	$C_6H_5C_7H_5O_3$	n. ins.	10	0.19 to 0.97 Gm.	3 to 15 grs.
Santonin	$C_{15}H_{18}O_3$	5000	40	0.06 to 0.19 Gm.	1 to 3 grs.
Scandium	Sc	..	..	....	....
Selenium	Se	..	..	....	....
Silica. See Silicic Oxid.					
Silicic Oxid	SiO_2	..	..	....	....
Silicon	Si	..	..	....	....

Abbreviations: s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]—(*Continued.*)

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Silver	Ag	ins.	ins.	....	....
" Bromid	$AgBr$	ins.	ins.	....	....
" Chlorid	$AgCl$	ins.	ins.	....	....
" Cyanid	$AgCN$	ins.	ins.	0.001 to 0.003 Gm.	$\frac{1}{60}$ to $\frac{1}{20}$ gr.
" Iodid	AgI	ins.	ins.	0.03 to 0.13 Gm.	$\frac{1}{2}$ to 2 grs.
" Nitrate	$AgNO_3$	0.6	26	0.008 to 0.03 Gm.	$\frac{1}{8}$ to $\frac{1}{2}$ gr.
" Nitrate (ammoniacal)	$AgNO_3 + 2NH_3$	..	..	....	....
" Oxid	Ag_2O	n. ins.	ins.	0.03 to 0.13 Gm.	$\frac{1}{2}$ to 2 grs.
" Sulphate	Ag_2SO_4	200	..	....	....
Sodium	Na	dec.	..	....	....
" Acetate	$NaC_2H_3O_2 + 3H_2O$	1.4	30	0.65 to 2.6 Gm.	10 to 40 grs.
" Acetate (dry)	$NaC_2H_3O_2$	v. s.	s.	....	....
" Arsenate	$Na_2HAsO_4 + 7H_2O$	4	sp.	0.0027 to 0.008 Gm.	$\frac{1}{24}$ to $\frac{1}{8}$ gr.
" Arsenate (dry)	Na_2HAsO_4	s.	sp.	....	....
" Arsenite (metarsenite)	$NaAsO_2$	s.	sp.	....	....
" Benzoate	$NaC_7H_5O_2$	1.8	45	0.65 to 3.9 Gm.	10 to 60 grs.
" Bicarbonate	$NaHCO_3$	11.3	ins.	0.65 to 3.9 Gm.	10 to 60 grs.
" Bisulphite	$NaHSO_3$	4	72	0.65 to 1.9 Gm.	10 to 30 grs.
" Bitartrate	$NaHC_4H_4O_6 + H_2O$	s.	ins.	....	• ....
" Borate	$Na_2B_4O_7 + 10H_2O$	16	ins.	0.32 to 1.9 Gm.	5 to 30 grs.
" Borate (dry)	$Na_2B_4O_7$	s.	ins.	....	....
" Bromate	$NaBrO_3$	s.	sp.	....	....
" Bromid	$NaBr$	1.2	13	0.65 to 3.88 Gm.	10 to 60 grs.
" Carbonate	$Na_2CO_3 + 10H_2O$	1.6	ins.	0.32 to 1.29 Gm.	5 to 20 grs.

Sodium Carbonate (dry)	Na_2CO_3	v. s.	ins.	0.32 to 0.97 Gm.	5 to 15 grs.
" Chlorate	$NaClO_3$	1.1	100	0.19 to 0.97 Gm.	3 to 15 grs.
" Chlorid	$NaCl$	2.8	n. ins.	0.65 to 3.88 Gm.	10 to 60 grs.
" Citrate	$2Na_3C_6H_5O_7 + 11H_2O$	v. s.	sp. s.	0.65 to 3 88 Gm.	10 to 60 grs.
" Citrate (dry)	$Na_3C_6H_5O_7$	v. s.	sp. s.	....	....
" Cobaltic Nitrite	$Co_2(NO_2)_6 6NaNO_2 + H_2O$	s.	..	....	....
" Hydrate	$NaOH$	1.7	v. s.	....	....
" Hypophosphite	$NaH_2PO_2 + H_2O$	1	30	0.32 to 1.29 Gm.	5 to 20 grs.
" Hyposulphite (dry)	$Na_2S_2O_3$	s.	s.	....	....
" Hyposulphite (thiosulphate)	$Na_2S_2O_3 + 5H_2O$	0.65	ins.	0.32 to 1.55 Gm.	5 to 24 grs.
" Iodid	NaI	0.6	3	0.32 to 3.88 Gm.	5 to 60 grs.
" Lactate	$NaC_3H_5O_3$	v. s.	v. s.	....	....
" Molybdate	$Na_2MoO_4 + H_2O$	..	..	....	....
" Nitrate	$NaNO_3$	1.3	100	0.52 to 2.59 Gm.	8 to 40 grs.
" Nitrite	$NaNO_2$	1.5	sl.	0.065 to 0.19 Gm.	1 to 3 grs.
" Nitroprussid	$Na_2Fe(NO)(CN)_5 + 2H_2O$	s.	..	....	....
" Phosphate	$Na_2HPO_4 + 12H_2O$	5.8	ins.	3.88 to 31 Gm.	1 to 8 drs.
" Phosphate (dry)	Na_2HPO_4	s.	ins.	....	....
" Pyrophosphate	$Na_4P_2O_7 + 10H_2O$	12	ins.	....	....
" Pyrophosphate (dry)	$Na_4P_2O_7$	..	..	....	....
" Salicylate	$NaC_7H_5O_3$	0.9	6	0.518 to 3.88 Gm.	8 to 60 grs.
" Santoninate	$2NaC_{15}H_{19}O_4 + 7H_2O$	3	12	....	....
" Sulphate	$Na_2SO_4 + 10H_2O$	2.8	ins.	3.88 to 31 Gm.	1 to 8 drs.
" Sulphate (dry)	Na_2SO_4	s.	ins.	....	....
" Sulphite	$Na_2SO_3 + 7H_2O$	4	sp.	0.65 to 3.88 Gm.	10 to 60 grs.
" Sulphite (dry)	Na_2SO_3	s.	sp.	....	....
" Sulphocarbolate	$NaC_6H_5SO_4 + 2H_2O$	4.8	132	0.518 to 1.94 Gm.	8 to 30 grs.
" Tartrate	$Na_2C_4H_4O_6 + 2H_2O$	5	ins.	....	....
Soziodol (soziodolic acid)	$C_6H_2I_2(OH)SO_3H$	..	..	....	....

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]—(*Continued.*)

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Spartein Sulphate	$C_{15}H_{26}N_2H_2SO_4 + 4H_2O$	v. s.	v. s.	0.008 to 0.065 Gm.	⅛ to 1 gr.
" Sulphate (dry)	$C_{15}H_{26}N_2H_2SO_4$	v. s.	v. s	....	....
Stannous Chlorid	$SnCl_2 + 2H_2O$	..	..	....	....
Strontium	Sr	..	..	....	....
" Bromid	$SrBr_2 + 6H_2O$	1.05	s.	0.32 to 0.65 Gm.	5 to 10 grs.
" Bromid (dry)	$SrBr_2$	s.	s.	....	....
" Iodid	$SrI_2 + 6H_2O$	0.6	s.	0.32 to 0.65 Gm.	5 to 10 grs.
" Iodid (dry)	SrI_2	s.	s.	....	....
" Lactate	$Sr(C_3H_5O_3)_2 + 3H_2O$	4	s.	0.32 to 0.65 Gm.	5 to 10 grs.
" Lactate (dry)	$Sr(C_3H_5O_3)_2$	s.	s.	....	....
" Nitrate	$Sr(NO_3)_2 + 4H_2O$	5	ins.	....	....
Strychnin	$C_{21}H_{22}N_2O_2$	6700	110	0.001 to 0.003 Gm.	$\frac{1}{60}$ to $\frac{1}{20}$ gr.
" Hydrochlorate	$C_{21}H_{22}N_2O_2.HCl$	50	s.	....	....
" Sulphate	$(C_{21}H_{22}N_2O_2)_2H_2SO_4 + 5H_2O$	50	109	0.002 to 0.005 Gm.	$\frac{1}{32}$ to $\frac{1}{12}$ gr.
" Sulphate (dry)	$(C_{21}H_{22}N_2O_2)_2H_2SO_4$	s.	s.	....	....
Sugar (cane-sugar)	$C_{12}H_{22}O_{11}$	0.5	175	....	....
" Grape (glucose)	$C_6H_{12}O_6$	s.	s.	....	....
" of Milk (lactose)	$C_{12}H_{22}O_{11} + H_2O$	6	ins.	....	....
Sulphonal	$C_7H_{16}S_2O_4$	500	65	0.3 to 1 Gm.	5 to 15 grs.
Sulphur	S	ins.	ins.	0.97 to 5.8 Gm.	15 to 90 grs.
" Dioxid	SO_2	s.	..	....	....
Tantalum	Ta	..	..	....	....
Tartar Emetic. See Antimonyl-Potassium Tartrate.					

Tellurium	Te	ins.	ins.	....	....
Terebene	$C_{10}H_{16}$	sl.	s.	0.18 to 0.62 c.c.	3 to 10 min.
Terpin Hydrate	$C_{10}H_{18}(OH)_2 + H_2O$	250	10	0.129 to 0.65 Gm.	2 to 10 grs.
Thallium	Tl	ins.	ins.	....	....
Theobromin	$C_7H_8N_4O_2$	sp.	s.	0.129 to 0.65 Gm.	2 to 10 grs.
Thiosinamin	$CS.N_2H_3(C_3H_5)$	..	..	....	....
Thorium	Th	..	..	....	....
Thymol	$C_{10}H_{13}OH$	1200	1	0.032 to 0.129 Gm.	½ to 2 grs.
Tin	Sn	ins.	ins.	....	....
Titanium	Ti	..	..	....	....
Tribromphenol	$C_6H_2Br_3OH$	ins.	..	....	....
Trional	$C_8H_{18}S_2O_4$	320	v. s.	0.3 to 1 Gm.	5 to 15 grs.
Tungsten	W	..	..	....	....
Tungstic Oxid	WO_3	..	..	....	....
Uranium	U	ins.	ins.	....	....
Urea	$CO(NH_2)_2$	1	ins.	....	....
Urethane	$C_3H_7NO_2$	s.	s.	0.6 to 2 Gm.	10 to 30 grs.
Vanadium	V	ins.	ins.	....	....
Vanillin	$C_8H_8O_3$	sp.	s.	....	....
Veratrin	$C_{32}H_{52}N_2O_8$	sp.	s.	0.002 to 0.006 Gm.	$\frac{1}{30}$ to $\frac{1}{10}$ gr.
Water	H_2O	..	..	....	....
Xylene (xylol)	C_8H_{10}	sp.	s.	....	....
Ytterbium	Yb	..	..	....	....
Yttrium	Y	..	..	....	....
Zinc	Zn	ins.	ins.	....	....
" Acetate	$Zn(C_2H_3O_2)_2 + 2H_2O$	2.7	36	0.032 to 0.129 Gm.	½ to 2 grs.
" Acetate (dry)	$Zn(C_2H_3O_2)_2$	s.	s.	....	....
" Bromid	$ZnBr_2$	v. s.	v. s.	0.065 to 0.129 Gm.	1 to 2 grs.
" Carbonate (official)	$(ZnCO_3)_2 + 3Zn(OH)_2$	ins.	ins.	....	....

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XX.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, SOLUBILITY, AND DOSE.[1]—(*Continued.*)

NAME.	SYMBOL OR FORMULA.	SOLUBILITY: 1 part dissolved in		DOSE.	
		Water.	Alcohol	Metric.	Apothecaries'.
Zinc Carbonate (pure)	$ZnCO_3$	ins.	ins.	....	....
" Chlorid	$ZnCl_2$	0.3	v. s.	....	....
" Iodid	ZnI_2	v. s.	v. s.	0.065 to 0.129 Gm.	1 to 2 grs.
" Oxid	ZnO	ins.	ins.	0.065 to 0.32 Gm.	1 to 5 grs.
" Phosphid	Zn_3P_2	ins.	ins.	0.004 to 0.02 Gm.	$\frac{1}{16}$ to $\frac{1}{8}$ gr.
" Sulphate	$ZnSO_4 + 7H_2O$	0.6	ins.	0.065 to 0.19 Gm. 0.648 to 3.88 Gm.	1 to 3 grs. 10 to 60 grs.
" Sulphate (dry)	$ZnSO_4$	v. s.	ins.	....	....
" Sulphocarbolate	$Zn(C_6H_5SO_4)_2 + H_2O$	s.	ins.	0.065 to 0.2 Gm.	1 to 3 grs.
" Sulphid	ZnS	ins.	ins.	....	....
" Valerianate	$Zn(C_5H_9O_2)_2 + 2H_2O$	100	40	0.03 to 0.129 Gm.	½ to 2 grs.
Zirconium	Zr	ins.	ins.	....	....

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XXI.—APPROXIMATE EQUIVALENTS.

1 Gm. } = 15.5 grains or minims.
1 c.c. }
1 milligram = $\frac{1}{64}$ grain.
1 Liter 1 quart (+).
1 Kilogram = 2.2 lbs.

1 grain or minim = 0.065 Gm. or c.c.
1 drachm 4.0 Gm. or c.c. (—).
1 ounce — 30.0 Gm. or c.c. (—).
1 pint — 0.5 Liter (—).
1 pound — 0.45 Kg. (+).

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ANALYTIC INDEX AND DOSE TABLE.

The *actions* of drugs and of their pharmaceutic preparations will be found under the English name of their main ingredient, or under the corresponding groups. The *materia medica* and the *doses* (in the Metric System) are usually given under the Latin name of each preparation. The main mention of each topic is indicated by *boldfaced type*.

P. W.* refers to the *experimental section ; C*, to chemic experiments ; *F*, to those on frogs ; *M*, to mammals. The *tests* will commonly be found under *P. W.—C.

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  aromaticum, 690.
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  ipecacuanhæ, 325..0.5 to 2.0
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  arseniosum (B.P.) [Arsenosum, U.S.P.], 582, **610,** 0.001 to 0.006
  benzoicum, **390,** 583, 0.1 to 0.5.
  boricum (boracicum), **575,** 582............0.3 to 1.0
  camphoricum, **468;** action, 464 to 466.......0.6 to 2.0
  carbolicum (and crudum and liquefactum), **387,** 583.

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[1] The pages refer mainly to the materia medica ; for the actions, see under "acids" and under the corresponding ions.

Acidum chromicum, 582, **585.**
  citricum, 583, **585**; as flavor, 125.
  formicum, 583, **586.**
  gallicum, 583, **678**. . 0.1 to 0.6
  hydriodicum, 583, **584.**
  hydrobromicum dilutum, 582, 584, **610** . . . . 5.0 to 10.0
  hydrochloricum (and crudum), 582, **583.**
    dilutum, 582 . . . . 0.1 to 1.0
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  lacticum, 583, **585.**
  muriaticum, 583.
  nitricum (also fumans and technicum), 582, **584.**
    dilutum, 582 . . . 0.10 to 1.0
  nitrohydrochloricum (nitromuriaticum), 582, **584.**
    dilutum, 582, **584** . . 0.10 to 1
  oleicum, 583, **587**, 743.
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    dilutum, 582, **584** . . 0.10 to 1
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[1] Fluidum (U.S.P.) = liquidum (B.P.).

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[1] Glyceritum = Glycerinum, B.P.

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[1] Dose of all essential oils: 0.1 to 0.3 unless specially noted.

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  chenopodii, 739, 0.1 to 0.60
  cinnamomi, 123, 689, **716.**
  copaibæ, 691 . . . 0.06 to 0.30
  coriandri, 123, **716.**
  crotonis, 719 . . . 0.015 to 0.12
  cubebæ, 690, **691,** 0.3 to 1.20
  erigerontis, **686,** 689, 0.05 to 0.30
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  catharticæ compositæ, 724.
    vegetabiles, 724.
  colocynthis composita, 724.
  ferri, 623.
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[1] Pilulæ = Pilula, B.P. (The dose of U.S.P. pills is one to five [B.P., 0.25 to 0.5]).

Pine bark, **690**.
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Pipsissewa, 387.....2.0 to 8.0
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    4.0 to 8.0
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    4.0 to 15.0
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  hypophosphis, 650,
    0.12 to 1.2
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[1] For the action of the potassium salts see the corresponding anions.

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[1] The dose of suppositoria is one to two.

[2] The dose of syrups is 2.0 to 8.0 c.c.

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[1] For action see main ingredient.

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  composita, 722.
  et myrrhæ, 722, 4.0 to 10.0
 amara, 715 ..... 4.0 to 8.0
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  florum, 689.
  radicis, 689.
 aromatica, 125, **690**, 1.0 to 4.0
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  amari, 124, **714**, 1.0 to 4.0
 dulcis, 124 ..... 1.0 to 4.0
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  foliorum, 264, 0.3 to 2.0
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  composita, 689, 2.0 to 4.0
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 buchu, 692 ..... 2.0 to 4.0
 calumbæ, 712 .. 4.0 to 15.0
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  composita, 124, **716**, 1.0 to 4.0
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[1] Trochisci = Troschiscus, B.P. (The dose of troches is one to four.)

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